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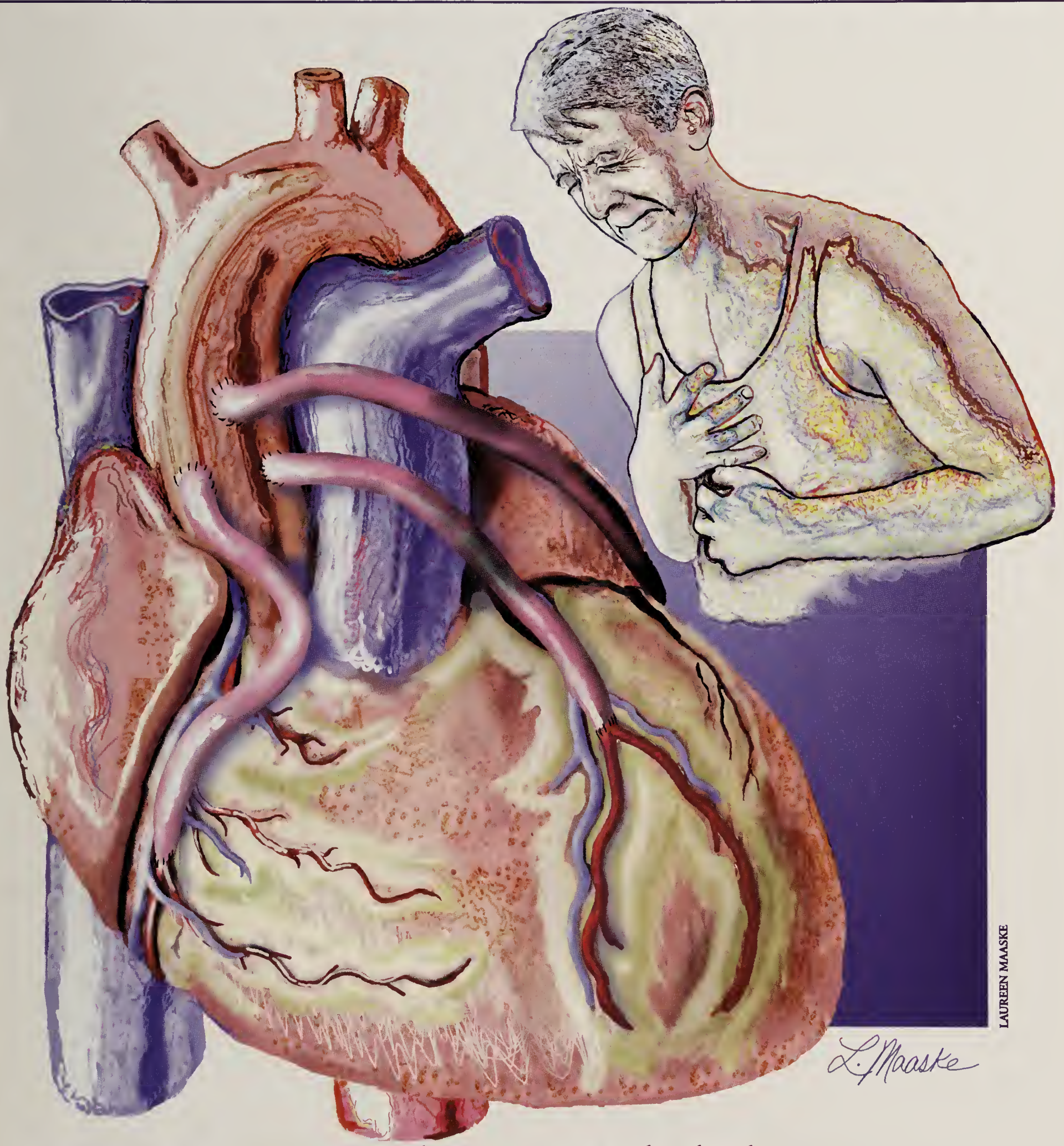
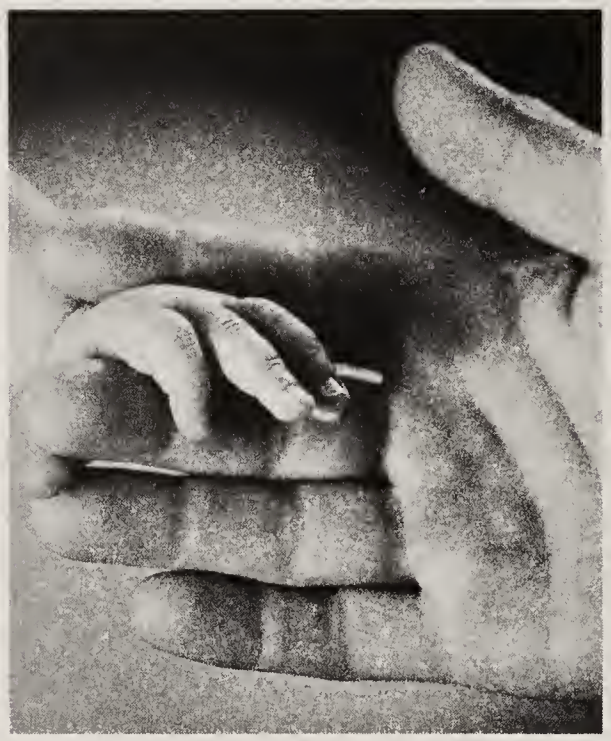


LAUREEN MAASKE

- Unstable Coronary Syndromes
- NSAID Induced GI Injury
- p53
- Functional MRI
- Medical Education
- VRE Outbreak
- Biomedical Communications
- Paediatrics Rounds

From small things good things grow.



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Front cover illustration by Laureen Maaske, Department of Biomedical Communications, University of Toronto.

Editorial

When we undertook the positions of Editors-in-Chief, we felt as though we had been given a unique opportunity. We wished to continue to cultivate the broad appeal of the University of Toronto Medical Journal that is engendered by the extensive range of high quality research that is routinely included. We interpret the mandate of the UTMJ as being extensive. This journal provides a forum for research and academic discourse and serves as an instrument for undergraduate medical students to initiate their careers as contributors to the medical literature. Furthermore, with its rich history as the oldest undergraduate medical publication in Canada, the UTMJ is a showpiece for the Faculty of Medicine and the University of Toronto. Naturally, we were humbled by the responsibility with which we had been entrusted; however, we have embarked on a year of innovation and of bold change and have, we hope, improved upon the legacy of this distinguished publication.

It takes but a glance at this, the third and final issue of volume #73 to recognize the evolution that has occurred over the past year. The Journal has grown in size and in scope. We have overhauled our format so that readers can now enjoy longer, more comprehensive articles. In issue #2, we moved to implement changes to the physical design of the Journal, starting with our new hard-bound spine. Issue #3 has a number of original features, including our redesigned *News & Views* section, and for the first time, the use of full colour to supplement our articles. We have also inaugurated a new section, the *Biomedical Communications Gallery*, as a showcase for the creative and educationally valuable contributions made by the individuals in that program. Furthermore, we have initiated a move to bring the Journal on-line and in the near future, people around the world will be able to access the UTMJ via the Internet. In addition to these developments for the Journal, with the help of the efforts of the UofT Medical Student Research Day committee, we were able to revise the design and format of our January Supplement.

In this issue, readers can consult the new *News & Views* section for information regarding the new Project Create initiative, as well as a variety of other news items. We also include two papers with special relevance to undergraduate medical education. The first addresses the topic of the recent trend in medical curricula toward education in community health and provides a critical analysis of the *Health and Illness in the Community* course at UofT. The second evaluates the role of computers and information technology in medical education. Finally, there is a timely paper which examines the problem of the emergence of multi-drug resistant disease strains and describes the recent experience with vancomycin resistant enterococci at Toronto's Mount Sinai Hospital.

This issue features the 1993 Department of Medicine Award winning article which was presented at the National Medical Student Research Forum in Galveston Texas. The paper, from the field of cardiology, evaluates various interventions in patients with previous coronary artery bypass grafts who present with unstable coronary syndromes. We also present submissions from the fields of gastroenterology and oncology. It is our pleasure to publish a paper from the area of neurology which won the George Brown Memorial Award at UofT Medical Student Research Day which was hosted at the Medical Sciences Building in January.

The *International Health* section provides two papers that chronicle the experiences of UofT medical students who have participated in the International Health Program and conducted research in developing countries. Readers may also join us on paediatrics rounds in the *Quick Diagnosis* section.

Publishing the University of Toronto Medical Journal is an enormous endeavor and represents the efforts of a multiplicity of people. The Editors would like to thank all of the authors who submitted articles this year. We acknowledge the contributions of our editorial staff and thank the remarkably talented individuals in the Division of Biomedical Communications for their outstanding illustrations. We also appreciate the patience and skill of the typesetters at Type & Graphics. Finally, we wish to extend our deepest gratitude to the patrons of the UTMJ whose ongoing support allows this Journal to endure and has made our enhancements possible.

We hope that next year's staff will find this experience as rewarding as we did and will continue to improve the Journal with their own style.

Mark J. Korman
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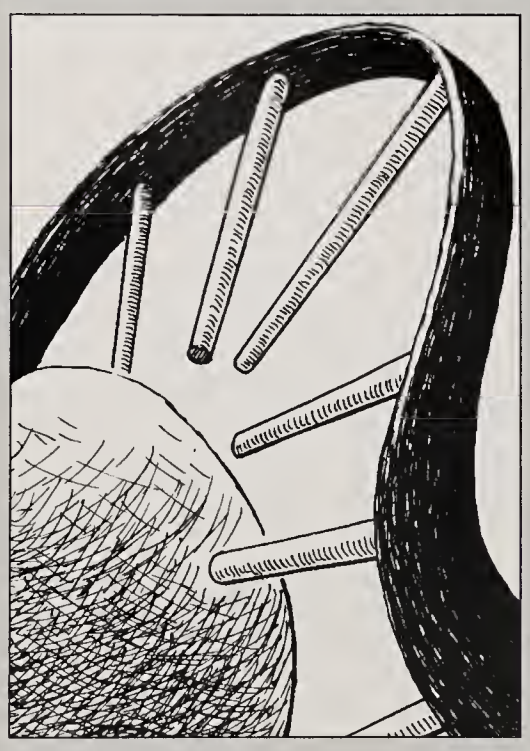
Suppressing HIV,One Enzyme at aTime

• On March 22, 1996 the first HIV protease inhibitor was approved for market distribution in Canada. The drug, saquinavir, is being sold under the trade name Invirase^{tm} (Hoffman-La Roche) and is intended for use in combination therapy with reverse transcriptase inhibitors. Such a treatment approach provides, for the first time, the ability to stop HIV replication at two distinct sites. "Among the advantages...is the potential to combat the virus's ability to quickly mutate and resist the drugs.", says Dr. Christos Tsoukas, Director of the Immune Deficiency Centre at Montreal General Hospital. Early this year, at the Third Conference on Retroviruses and Opportunistic Infections in Washington, another protease inhibitor, Indinavir (Merck & Co.) in combination with 3TC (BioChem Pharma, Laval, Glaxo Wellcome) and AZT (Glaxo Wellcome), showed the greatest effects on HIV replication seen to date. Such promising results have paved the way for a new approach to combination therapy.



JOHN HARVEY

Raising Awareness about Substance Abuse in Ontario Medical Schools

Karen Gronau, MSc. (9T8)

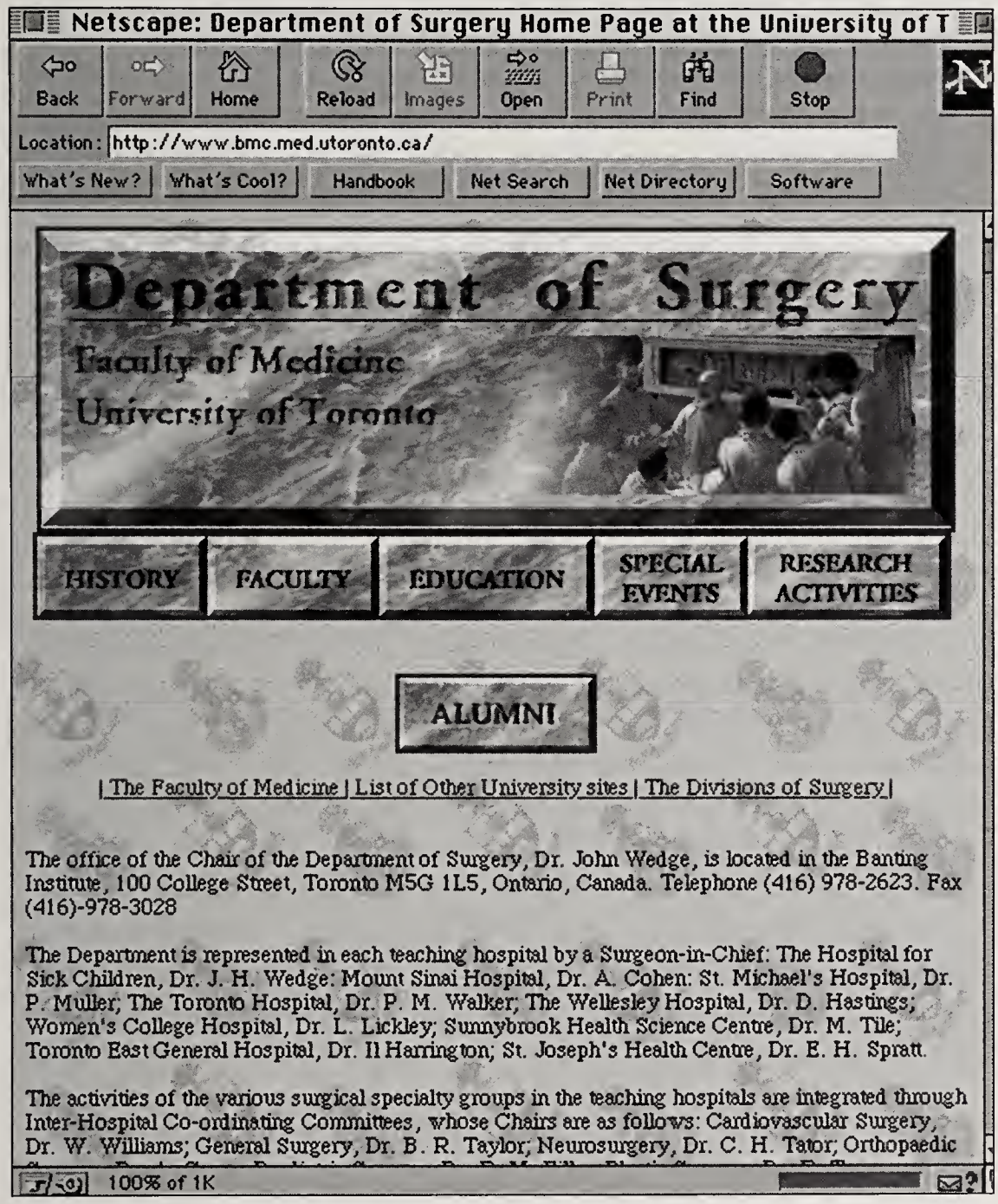
The Addiction Research Foundation and the Lawson Foundation have recently funded a five year educational initiative involving all five Ontario medical schools. The program, called Project Create, is committed to the development, implementation and evaluation of an interdisciplinary undergraduate medical curriculum on alcohol and drug use. In addition, a program for the prevention and management of substance use disorders among medical undergraduates and faculty will be developed. The principal investigators of the project are Drs. Meldon Kahan and Lynn Wilson. The Associate Deans of Undergraduate Studies at each medical school will serve as co-investigators.

A task force for curriculum and a site co-ordinator will be appointed at each medical school. As interschool collaboration is to be strongly emphasized, province-wide task forces will also be established. The interdisciplinary aspect of this project is vital; thus, faculty and community experts, physicians and medical students from each site are encouraged to participate. There are various ways to get involved, including: ongoing project planning and evaluation, teaching new components of the curriculum to medical undergraduates, and developing community placements that will serve to enrich the educational process. Individuals with a particular interest in any of these areas are invited to join the Project Create team. Medical students are especially encouraged to join the project. They can be directly involved in curriculum changes, and are also invited to help develop the physician impairment programs. It is also possible that medical student involvement can be effected through school projects.

A meeting of the steering committee took place at the College of Family Physicians of Canada on April 11th. At the meeting, overall and site-specific progress reports were delivered, followed by task force objective planning and small group meetings around these objectives. Members of the steering committee will meet periodically over the next five years to discuss the overall development and direction of the program from both local and provincial perspectives. Anyone interested in attending these meetings would be expected to be actively involved in developing an identity for Project Create at one of the five sites and to participate on one of the Task Forces. People interested only in working on a Task Force are not required to attend steering committee meetings. Rather, they will work on the project locally, interacting with the site co-ordinator and the chair of the Task Force they are involved in. Any medical students or faculty interested in joining Project Create in any capacity, or anyone interested in obtaining more information about the program can contact the project director, Deana Midmer, at (416)767-8004 or by e-mail at deana.midmer@utoronto.ca

Medicine and the Internet

Robert Yu, BSc. (9T8)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The activities of the various surgical specialty groups in the teaching hospitals are integrated through Inter-Hospital Co-ordinating Committees, whose Chairs are as follows: Cardiovascular Surgery, Dr. W. Williams; General Surgery, Dr. B. R. Taylor; Neurosurgery, Dr. C. H. Tator; Orthopaedic
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BRYCE HOUGH AND DINO PULERÀ

Medical Education

Imagine, if you will, the year 2020. A successful family physician, you sit in front of your personal computer and access the latest edition of JAMA through the Internet. You scroll through the articles and find an interesting research study on the role of functional radiology in detecting early lung cancer. You notice that the article was submitted to the editors only one week ago. The text is clear and easy to follow, but you are unable to recall the principles of functional radiology. You click on the bolded words "functional radiology" and switch your Net browser to 3D mode. Instantaneously, the screen fills with a graphical tutorial on PET and SPECT and provides you with 3D images of normal brain and lungs. The computer queries if you would like to observe the database of brain pathology collected from the labs of researchers from around the world. As you are about to answer, a call signal arises on your screen and the face of your colleague in northern Canada appears. She has called to obtain

Alcohol Dependence Drug Approved

• A new pharmaceutical treatment for alcoholism has been approved for use in Canada. Naltrexone, an opioid-receptor antagonist, is being marketed under the trade name ReVia(from Dupont Pharma. The definitive paper by Volpicelli, et al. in the Archives of General Psychiatry (Nov. 1992) demonstrated a significant decrease in the relapse rates among patients treated with naltrexone. Also, among patients who drank during the study, only 50% of patients on naltrexone relapsed to heavy drinking, as compared to 95% among placebo-controls.

Previous pharmaceutical strategies, using disulfiram and calcium carbimide, have centered around aversion therapy. Naltrexone, on the other hand, has been shown to reduce cravings for alcohol. Its mechanism of action may be explained by recent studies which suggest that alcoholism is associated with beta-endorphin activity in the brain. Dr. Ed Sellers, of the Addiction Research Foundation, explains that "Opioid antagonists, such as naltrexone, have been shown to block the effects of beta-endorphins and decrease the need for alcohol".

Alcoholism affects 1.7 million Canadians and costs the public an estimated $11.9 billion dollars. Sobering figures indeed.

UTMJ Article Wins Award

• **Derek Plausinis** (9T8) has been awarded the R.I. Harris Undergraduate Award - Orthopaedic Surgery for his article entitled "The Use of Pedicle Screws in Spinal Fusion: FDA Approval and Current Controversy". His award will be presented at the annual Kennedy Visiting Professor Day hosted by the Division of Orthopaedic Surgery at the University of Toronto.

St. Michael's Hospital's new Simulated Trauma Mannequin took over 2 years to develop, and is the first of its kind in the world.

Robo-Patient At St. Mike's

• On April 9, 1996 St. Michael's Hospital unveiled the world's first Simulated Trauma Mannequin (STM). Designed by CAE Electro-nics Inc., the STM is equipped with internal systems representative of the trachea, bronchial tree, esophagus and lungs. It also has a speaker system to simulate heart sounds, breath sounds, and a human voice. This $250,000 patient is also equipped with devices designed to simulate femur fractures, and intracranial and thoracic trauma. Moreover, the mannequin has built in software to react to various treatment and medications.

The artificial patient will be used to train trauma teams at St. Mike's. As Dr. James Waddell, Medical Director of Trauma Services explained, "Now, medical professionals will be able to administer drug dosages, perform diagnostic procedures and practice surgical techniques without the risk of potential harm to a patient. It will make a tremen-

your opinion on a skin lesion found on one of her patients. Staring intently at the image on the screen, you are unsure of the answer. With an apologetic glance at the camera mounted beside your computer, you give her the video-mail address of an excellent dermatologist that you know.

Science fiction or probable science fact? The scenario describes technology that exists now. Although crude and still in its infancy, the Internet represents a communications and information tool with endless possibilities. It frees physicians and medical students from the constraints of an antiquated educational system predicated on the memorization of ever-increasing medical data. Like problem based learning, the use of the Internet fosters the development of new knowledge and skills that enable individuals to access a broadening array of resources and services.

"Although crude and still in its infancy, the Internet represents a communications and information tool with endless possibilities."

It is clear that medical educators are aware of the importance of computers and networked information in the teaching of medical students. At the University of California at Davis, education in the area of electronic communication such as E-mail, Newsgroups and Internet file searching has been mandated as one of four required classes in the second year of the medical curriculum[1] . Despite some initial resistance and difficulty, as the changes took hold in the pilot year the students found that the Internet skills they gained were valuable. At the Medical College of Pennsylvania in Philadelphia, computers were used to teach cardiac auscultation, incorporating both visual and auditory aids. Educators there felt that by providing both a visual and auditory database for cardiac auscultation, students would receive a greater opportunity to encounter (at their own leisure) the wide variety of patients that is required to develop and maintain proficiency. Although the sample sizes were small, comparison studies showed that those students that learned using the computer teaching aid had diagnostic scores that were 5-10% greater than their non-computer peers[2]. Finally, at the Case Western Reserve University in Cleveland, medical educators so strongly believed in the importance of computers and their role in education that they ensured computer access for all students by providing each with a portable computer upon entering medical school[3] .

When considering all of the research and opinions that favour the increasing use of computer technology, it becomes apparent that medical schools should incorporate the teaching of computer skills into their curriculum if they have not already done so. At the University of Toronto Faculty of Medicine, teaching computer literacy is not part of the current curriculum. Instead, knowledge of computer databases is gained from voluntary experimentation with school resources and participation in informal training sessions.

With all of the technology and services available through the Internet, it is not surprising that medicine has taken advantage of this information tool. There now exist discussion groups on various topics ranging from colorectal research to alternative medicine; teaching files for numerous specialties and

disciplines; and journals such as the British Medical Journal and the New England Journal of Medicine. Newsgroups, allow physicians and students to discuss specific concerns or new ideas with minimal time delay. Graphic capabilities enable faculties and specialties to provide databases for continuing medical education and enhanced text-based information.

The capability to digitally scan images, to enhance text with graphics, and to provide universal access have led many to consider the World Wide Web as an attractive medium for radiology education. The University of Washington at Seattle brought their teaching files on-line in 1994[4] (http://www.rad.uwashington.edu/) as did the University of Iowa[5] (http://vh.radiology.uiowa.edu/). In a relatively short time they have made their image files available on the Internet, free for anyone to access. X-ray, CT or MRI scans, anatomy lessons, and various joint movements can all be visualized through access to these radiology teaching files. Increased use of fiberoptic cables and the falling costs of installing personal lines, will improve image quality and fidelity as well as increase the speed of transmission.

"With the widespread adoption of new technology and software, medical education may become decentralized from large institutions . . ."

Another educational application of the Internet has been the digital manuscript. Digital manuscripts are articles and journals created and transferred in an electronic format which contain all the components of traditional paper-based documents but they may contain features such as digital video and audio. The potential benefits of digital manuscripts include the facilitation of collaboration among authors, faster and more convenient peer review, and the use of multimedia to convey information[6] . There are currently many paper journals that have digitized their manuscripts for the Internet. These include such prestigious titles as the British Medical Journal, the Journal of the American Medical Association and the New England Journal of Medicine. The BMJ also has an on-line journal for medical students titled the Student's BMJ. Currently, most of the medically related journals are electronic reproductions of the original paper articles and fail to take advantage of the features that a digitized article on the Internet could provide.

Some of the more liberal research journals provide hypertext and graphical connections to related Webpages, and documents of similar interest. Unfortunately, with no censorship of information it is difficult to distinguish reputable research from that which does not conform to established standards. Consequently, the peer-review process must maintain a critical role in upholding the integrity of research. In addition, copyright difficulties have restricted the extent to which peer-reviewed journals can accept E-mail submissions as the inadequate security of data on the Internet provides opportunity for the alteration or theft of information. Furthermore, in the Uniform Requirements for Manuscripts[7], it states that permission for

dous difference in how we train people in trauma care."

Since its inauguration in 1984, St. Michael's Hospital's Trauma Centre has cared for over 2500 victims.

Higher Tech Cardiology

• A number of new technological devices recently released by Hewlett-Packard promise to help streamline the practice of cardiology. Most notable is the new Acute Cardiac Ischemia Time-Insensitive Predictive Instrument™ (ACI-TIPI), which integrates patients' historical data, ECG recordings, and a database of medical case reports to predict the probability of acute cardiac ischemia. This information can help triage patients who truly require acute coronary care. A multi-center study in the American Journal of Medicine (Nov. 1989) showed that up to 50% of patients who were treated for ACI did not have it. It is hoped that ACI-TIPI can reduce this number, and save precious resources.

Another interesting product released is the ECGstat™ designed to allow emergency room clinicians to transmit full 12-lead ECG data, including waveforms, computerized analysis and patients notes, to cardiologists outside the hospital. This is especially good news for physicians in rural communities.

illustrations is always required unless the documents are designated as public domain. Are graphics on the Internet considered public domain? Will or do authors have the right to determine if certain words in their articles can be modified to hypertext and linked with other authors, articles, thoughts or illustrations? These are some of the issues that must be resolved before the full advantages of the Internet can be realized.

The Internet is a tremendously powerful resource with enormous application for medical education. Like all innovations, however, the possibilities and usefulness of the information superhighway have been slow to materialize. With the widespread adoption of new technology and software, medical education may become decentralized from large institutions, and arrive in the homes of every physician and student.

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Internet Addresses

Everyday new Webpages are added to the Internet. Some are strictly the attempts of schools or organizations to get onto the Net and serve no real resource value. Other pages are very ingenious and useful but may be difficult to find among the sea of information. The following are the URL's (Uniform Resource Locator) of some interesting or helpful medical Webpages. Several have been taken from the "The Internet Golden Directory"[8] which may be available in the Undergraduate Medical Education Office at the University of Toronto, Faculty of Medicine.

Directory of Healthcare Info Sites	http://www.achoo.com
Web of Addictions: addiction studies	http://www.well.com/user/woa/
AIDS Frequently Asked Questions	http://www.cis.ohio-state.edu/hypertext/faq/usenet/aids-faq/top.html
Alternative Medicine Home Page	http://www.pitt.edu/~cbw/altm.html
3D Medical Imaging	http://www.uni-hamburg.de/~medizin/imdm
NUS Histonet	http://biomed.nus.sg/HIS/HIS.html
Whole Brain Atlas	http://www.med.harvard.edu/AANLIB/home.html
Interactive Patient	http://medicus.marshall.edu/medicus.html
The ER Home Page	http://www.seas.gwu.edu:80/student/danny/er/
BCM Gene Finder	http://dot.imgen.bcm.tmc.edu:9331/gene-finder/gf.html
Genome Data Base	http://gdbwww.gdb.org/
CDC	http://www.cdc.gov
Interactive Medical Student Lounge	http://falcon.cc.ukans.edu:80/~nsween/
Virtual Hospital	http://indy.radiology.uiowa.edu/VirtualHospital.html
Neurosciences on the Internet	http://ivory.lm.com/~nab
British Medical Journal	http://www.bmj.com/bmj/
JAMA	http://www.ama-assn.org/journals/standing/jama/jamahome.html
NEJM	http://www.welch.jhu.edu/resources/dbs/nejm.html
Biomedical Communications	http://www.bmc.med.utoronto.ca
UofT Department of Surgery	http://www.surg.med.utoronto.ca
Surgical Infection Society	http://www.surgicalinfection.org
NKAOS Website Design	http://www.nkaos.com

Making it Matter - Public Health Education At The University of Toronto Medical School

Jordan Weinberg, BA (9T9)

Abstract

Recent trends in medical education have included support for replacing the traditional biomedical model of disease with a more holistic model that emphasizes education in public health. Public health studies, however, have historically faced apathy from medical students. Part of the University of Toronto Medical School's curriculum revision of 1992 included a new direction in public health education in a course entitled Health, Illness, and the Community. This paper addresses the historical student resistance to public health study and reviews the success of the Toronto program in this context.

"Primarily interested in treating illness on an individual basis, population-based care has proved an abstract and illusive concept for most."

Over the past decade, medical educators have advocated the replacement of the traditional biomedical model of disease with a broader "biopsychosocial" model. The newer model emphasizes the integration of public health and community care instruction with the basic sciences and clinical studies in the undergraduate medical curriculum.[1,2] Public health studies, however, have historically faced apathy from medical students.[3,4] At the University of Toronto, *Health, Illness, and the Community (HIC)*, an integral course of the medical school's revised curriculum of 1992, was created to provide education in the domains of public health and community care. The course has a student-centered format that encourages the acquisition of "biopsychosocial knowledge, skills, and attitudes about the range of appropriate, acceptable, effective and affordable approaches to the health of individuals and communities."[5] This paper addresses student resistance to public health instruction and reviews the success of the *HIC* course in overcoming it.

In 1910, Abraham Flexner, in his famous report on the state of medical education in North America, predicted the physician's function would become "social and preventive," rather than "individual and curative."[6] "Individual and curative," however, would set the tone for most of the century with the evolution of hospital-based medicine. Traditionally, medical students have considered public health to be a non-essential topic. Primarily interested in treating illness on an individual basis, population-based care has proved an abstract

Arthritis Patients, not Meteorologists

• In a recent publication of the *Proceedings of the National Academy of Science*, Dr. Donald Redelmeier of Wellesley Central Hospital, has challenged the age old relationship between arthritis pain and weather patterns. The study involved 18 patients with rheumatoid arthritis, most of whom believed their pain was influenced by weather, over a one year period. The data revealed no significant correlation between symptoms and weather. Dr. Redelmeier explains, "People look for changes in the weather when they experience an increase in pain and pay little attention to the weather when their arthritis is stable. A striking coincidence is impossible to forget." He adds, "People's belief about arthritis pain and the weather may tell more about the workings of the mind than of the body."

JOHN HARVEY

Help for the Homeless

• On March 29th, 1996 the University of Toronto, and the OMA held a workshop to address the growing problem of the health of the homeless. Homelessness in Ontario is increasing, and includes a higher proportion of teens, women and children. Many of these people dwell in substandard shelters. The workshop brought together doctors and other relevant health care workers to identify, and develop strategies to eliminate, the barriers to health care for this population.

JOHN HARVEY

"Adult Acne" Awareness

• The month of March, was designated as Rosacea Awareness Month in an attempt to increase early detection and treatment of this embarrassing and potentially disfiguring condition. Rosacea, which affects an estimated 2 million Canadians, is also called "adult acne", however it bares no etiologic connection to its adolescent counter-part. The most renowned rosacea sufferer was W.C. Fields, who owed his erythematous swollen nose to this disease. While there is no cure for

and illusive concept for most.[7] In The Threat and The Glory - Reflections on Science and Scientists, Peter Medawar wrote:

> "ordinary medical students tend to be bored by and are even a little contemptuous of the study of social medicine and public health ... the feelings of compassion that are thought to tempt young students into medicine soon make them realise that it is individual people not populations that are ill and in need of treatment."[4]

The apathy described can likely best be attributed to a medical education historically confined within hospital walls, allowing for little consideration of the communities outside.

As the end of the century approaches, health care policy advisors and educators claim this attitude to be outdated, and now call for the necessity of a social perspective in medicine and the appropriate educational foundation to foster this perspective. In 1993, the Education Committee of the General Medical Council (Great Britain) issued a document outlining the developing shift from hospital-based services to those provided in general practice and the community, and recommended changes to the undergraduate medical curriculum including an emphasis on instruction in public health.[1] In the United States, a similar position has been proclaimed.[2] Many countries, Canada included, are evaluating the concept of allocating health service funds according to population-based needs rather than a clinical, individual basis.[3] In such a scenario, doctors would require an appreciation and understanding of the elements of public health more so than ever before to provide effective care for their patients.

At the University of Toronto, the *HIC* course was created for the purpose of cultivating this appreciation and understanding in future doctors. Its mission is to foster

> "a fundamental transition in the scope and perspective of medical education from its traditional approach of being physician-centered, disease-oriented and institution-based to an integrative and comprehensive approach which is characterized by being person-oriented, community-centered, and population-focused."[5]

Essentially, the course comprises various community experiences in the domains of public health and community care. Working in partners and small groups, students relate to each other their experiences in small-group discussions and in formal presentations. The course is largely student-centered, allowing students much choice and self-direction. In the second year, students choose their own project in which they work within the community, perform research, and present their findings at the close of the course.

By taking its subject matter beyond the isolated classroom and allowing students to explore public health in their own community, the HIC course provides a dynamic and innovative framework for learning. The course provides students with an overview of public health and community care while promoting positive interaction with members of the community and among themselves. Instead of receiving a formal lecture on the Home Care Program of Metro Toronto, for example, students actually interview the care givers and patients involved. Field placements such as this encourage participation and are intuitively more valuable and memorable to the student than didactic lectures.

Student pairs within small groups of six visit different agencies and bring back their unique experiences to share with the group. Unfortunately, owing to the wide variety of health-related agencies that participate, there is a perceived heterogeneity in the value of the field experiences. This is largely uncontrollable, depending on the agency, the staff, and the clientelle on the day of the placement. It is, however, a shortcoming of the course. The student placed at a drug rehabilitation clinic, for example, could witness the ordeal of addiction and begin to appreciate the broad health issues surrounding drug addiction. The student, however, who is placed in a community day care, is unlikely to have such an eye-opening experience. Of course, these examples are extreme, but they illustrate the disparity of experience inherent in the structure of the course.

Perhaps the most significant deficiency in the course is its failure to clearly articulate the physician's place in the broad-based biopsychosocial model. Students would benefit from observing physicians implement public health principles in practice. The course involves many physicians in the roles of lecturers and tutors, but the community experiences tend to pair students with other types of health workers. Although there are obviously many benefits to working with non-physician care givers, directly observing doctors at work in the public health domain might provide both inspiration to some students and a clarification of the physician's role for others.

These faults notwithstanding, the HIC course exemplifies a progressive and impressive approach to the subject of public health. The "hands on" modality represents a fulfilling and enjoyable way to study this subject. Measures can be taken to remedy the problems outlined above. Although disparity among student experiences in field placements is inherent to the structure of the course, course coordinators must scrutinize the placement sites to ensure a measurable level of relevance to a student's medical education. Student feedback is being compiled and, over time, it should become clear as to which placements are of limited value to the student body. The physician's role can be better defined, simply by introducing some element of physician "role models" into the syllabus. If actual field placements with physicians are unfeasible, small-group workshops with doctors who incorporate public health principles into their practices could provide some elucidation of the physician's role. Overall, in the *HIC* course Toronto educators have laid a solid framework for communicating the relevance of public health study to students. Further development around the medical practice of public health will ultimately allow the course to accomplish its mission.

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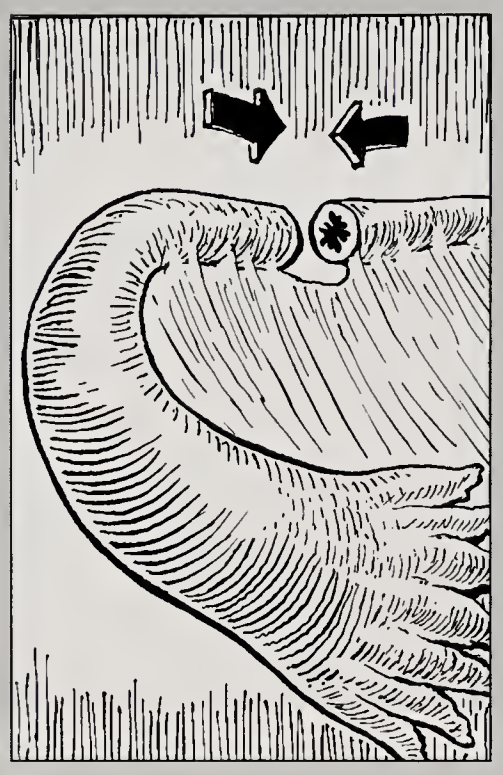
this chronic condition, the "progression of the disease can be arrested and the symptoms reversed through medical therapy and lifestyle modifications.", according to Dr. Neil Shear, Director of Clinical Pharmacology at UofT and Sunnybrook Health Sciences Centre. Individuals seeking further information may call 1-888-ROSACEA.



JOHN HARVEY

Nothing in Life is Forever

• Physicians at St. Luc Hospital (Montreal, Quebec) have developed a technique which has made it easier for patients to reverse a tubal ligation. Many regretful patients may now restore tubal patency with a laproscopic procedure. Dr. Francois Bissonnette, chief of reproductive endocrinology at St. Luc remarks that "It's too early to say how successful it will be...the pregnancy rate could be 70-80%, about the same as with the older technique." The new procedure takes just over an hour, patients are discharged the same day, and recover in one week. In contrast, the classic procedure lasts 3-4 hours, requires hospitalization for three to four days, and recovery takes up to six weeks. (Medical Post, Feb. 6, 1996.).

Ilan Lenga (9T8)

VRE - Outbreak at Mount Sinai Hospital

Ilan Lenga (9T8)

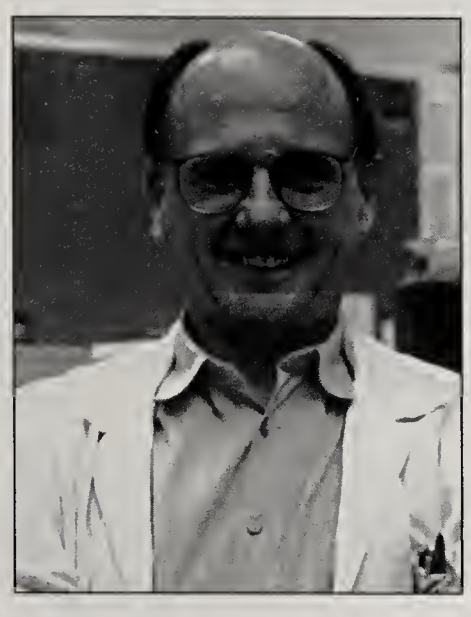
BRYCE HOUGH

The concept of antibiotic resistance, is an issue on which we rarely enjoy dwelling. Most of us conceptualize it as we would global warming or acid rain: inevitable and unfathomable. Our complacency regarding such global endangerments stems from years of blissful ignorance, and our innate ability to ignore issues which occur over a protracted time course. Our myopic vision of the future may reflect a pessimism which prevents us from considering long-term implications, or it may be that the global community is simply in a state of denial. Our complacency however, is more likely rooted in an optimistic reliance on the power of new technology. We are assured by pharmaceutical companies that they stand on the cutting edge of research, and that new antibiotics are on the way. We are comforted by immunologists perfecting vaccines for bacteria and viruses alike. We look to evidence from studies regarding Pneumococcal and Haemophilus vaccines as proof that pathogens can be conquered. We have been lulled into a sense of security by sixty years of success with a formidable arsenal of antimicrobials.

Yet bacteria, rarely daunted by a confident stance and an impressive track record, continue to wage war through their singular biological purpose - survival. Bacteria continue to mutate, acquire transposons, and undergo transformation regardless of the number of them that we kill. They are, in essence, an unconquerable army - persistent and merciless. Worst of all, it appears that the more potent our attack, the more obdurate the remaining population becomes.

Tuesday Feb. 13th	**Friday Feb. 16th**	**Sunday Feb. 18th**	**Mon. - Tues. Feb. 19th-20th**	**Thurs.-Fri. Feb. 22nd-23rd**
Canadian patient from the Cleveland Clinic in Ohio is transferred to MSH for treatment of post-operative infections.	Infection is realized to have been contracted in the U.S. Patient is investigated for MRSA and VRE.	MRSA infection is detected; patient put in isolation	VRE colonization is detected in the patient. Patients on the floors he has come in contact with (11 and 14) are screened with peri-rectal swab.	One secondary colonization is found on the 14th floor.* The ward is isolated by Friday afternoon.

*How did they know it was a secondary colonization? Mount Sinai Hospital has had a screening program in place for some time, and was considered VRE-free. Molecular analysis confirmed that the secondary case(s) were indeed from the same index case.



Dr. Don Low. Microbiologist-in-chief at the Mount Sinai Hospital spearheded the initiative to control the VRE outbreak last February

As early as 1950, doctors realized that certain strains of bacteria were becoming antibiotic resistant[1]. "Becoming" resistant is somewhat of a misnomer, as scientists have always agreed that although these strains arose spontaneously, their proportion in the bacterial population was increasing as a result of selection pressures imposed by antibiotics. In a sense, we were killing all of the weak bacteria and allowing the strong to flourish. Since then resistance has been on the rise. One of the first organisms recognized for its resistance was Staphylococcus aureus. Staph. is a pathogen known to cause infection in nosocomial settings in post-operative and immunocompromised patients. Penicillin lost its effectiveness for treating S. aureus infections and in response, scientists developed methicillin. Rapidly, Methicillin-Resistant-Staphylococcus aureus (MRSA) emerged which could only be treated with Vancomycin.

Vancomycin was discovered in 1954 and is a glycopeptide, cell wall active, drug. This means that it interferes with cell wall synthesis in gram positive bacteria by binding to the terminal D-alanine (D-ala) of the peptidoglycan subunit. This interaction sterically inhibits synthesis of the cell wall, thereby producing a bactericidal effect.

Microbiological Resistance

VRE, or Vancomycin Resistant Enterococcus, is a strain of Group D Streptococci (Enterococcus) that are impervious to Vancomycin's effects. VRE was first described in France in 1988, and has since become globally disseminated.[2] While normal Enterococcus is indigenous to the gut, VRE represents a devastating new resistance, as Vancomycin is considered to be the last line of defence against gram positive bacteria. The molecular basis for this resistance rests in a 10kb transposon that encodes a number of genes, of which three have been well characterized and their enzymatic products named: Van-H, Van-A, and Van-X. These enzymes work together to create an altered cell wall in which the terminal D-ala is replaced with a D-lactate. Vancomycin is unable to bind with D-lactate, rendering the drug useless. Unfortunately, this abnormal cell wall appears to be stable and does not adversely affect the function of the organism.

Particularly disturbing is that in-vitro experiments have demonstrated that if the VRE transposon is introduced into MRSA, it is well expressed. This implies that Vancomycin resistance can be transferred from Enterococci to other gram positive bacteria. Most feared are MRSA (creating a VRMRSA), and Streptococcus pneumoniae. Strep. is the most common cause of community-acquired pneumonia, and is a cause of pharyngitis associated with non-suppurative complications. Already there have been isolated reports of multi-drug resistance strains of these bacteria.

VRE in the community is not as problematic as in the hospital setting for a number of reasons. Firstly, the natural flora of the GI tract prevents infections under normal circumstances. In hospitalized patients, this flora is often altered by antibiotic administration. Secondly in a larger population the prevalence of colonization is decreased due to a dilution effect. Finally, VRE is often naturally cleared by immunocompetent hosts.

Is VRE Unstoppable?

VRE itself is not an aggressive pathogen. Being colonized with VRE is not synonymous with being infected. VRE colonizations are asymptomatic, usually self-limited, and often cleared spontaneously by the host. Infection only occurs in immunocompromised or elderly persons, and refers to excessive and symptomatic replication of the bacteria. VRE is found in the GI tract, but can survive for prolonged periods in the environment. It has been detected on stethoscopes, bed rails, BP cuffs, patients sinks, etc. Since it is readily communicable, VRE can wreak havoc in nosocomial environments, and ultimately infect immunocompromised patients. In order to facilitate clearance of VRE, microbiologists have employed Bacitracin, a rarely used

Saturday Feb. 24th	**Sunday Feb. 25**	**Monday Feb. 26th**	**Friday March 1st**
Two more cases are discovered on 11th floor. Isolation procedures are put into effect.	One more case found on 11th floor.	Situation under control. Hospital-wide screening put into effect. No new cases are found. Patients on affected floors, who are clear of VRE, are discharged. Floors are sterilized	Results from a second screening are obtained: no new cases are found.

antimicrobial. In other outbreaks, including last year's experience at the Toronto Hospital, teichoplanin, another glycopeptide antibiotic imported from France, has been used. Use of teichoplanin is reserved for infected cases because it can potentially lead to further drug-resistance. Other anti-microbials are currently under investigation.

The Outbreak

Earlier this year, the Mount Sinai Hospital (MSH) in Toronto was given a dramatic reminder of the speed and cunning of VRE in nosocomial environments. On Feb 13th, 1996, a Canadian patient was transferred from the Cleveland Clinic in Ohio to MSH for treatment of post-operative infections developed subsequent to coronary bypass surgery. It was not, however, until three days later that this patient was screened for MRSA and for VRE known to be endemic in most urban hospitals in the U.S.[3] By that time, the patient's VRE had spread to other patients on two floors. VRE proceeded to colonize four other patients, and prompted an immediate response by the infection control team at MSH. While misrepresented in the media as VRE infections, the MSH, under the direction of microbiologist-in-chief Dr. Don Low, instituted extensive measures to contain the colonization and prevent VRE from infecting immunocompromised patients.[4] Dr. Low remarked, that while the situation was well controlled and the threat eliminated, this experience has served as a reminder to Canadian physicians that "VRE is on the way." (See Timeline for further details).

Prevention

Prevention appears to be best accomplished through education. Doctors must be advised to deny patients antibiotics on request. According to Dr. Low, this change in prescribing practices could reduce antibiotic use by 30%. Patients should also be educated not to expect a "pill for every ill". Furthermore, indiscriminate use of antibiotics in animal feed also selects for resistant strains; it is postulated that VRE may have arisen due to injudicious use of a Vancomycin-like antibiotic used in animal feed. In short, prevention begins with a change in attitude regarding antibiotic use.

"...The best way to slow down the spread of multi-drug resistant bacteria is to stop inappropriate use of antibiotics.", says Dr. Low. "We have to start doing studies to define when we need antibiotics."

The UTMJ and the author are indebted to Dr. Don Low, Microbiologist-in-Chief at Mount Sinai Hospital, for providing information for this article.

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The Management of Unstable Coronary Syndromes In Patients With Previous Coronary Artery Bypass Grafts

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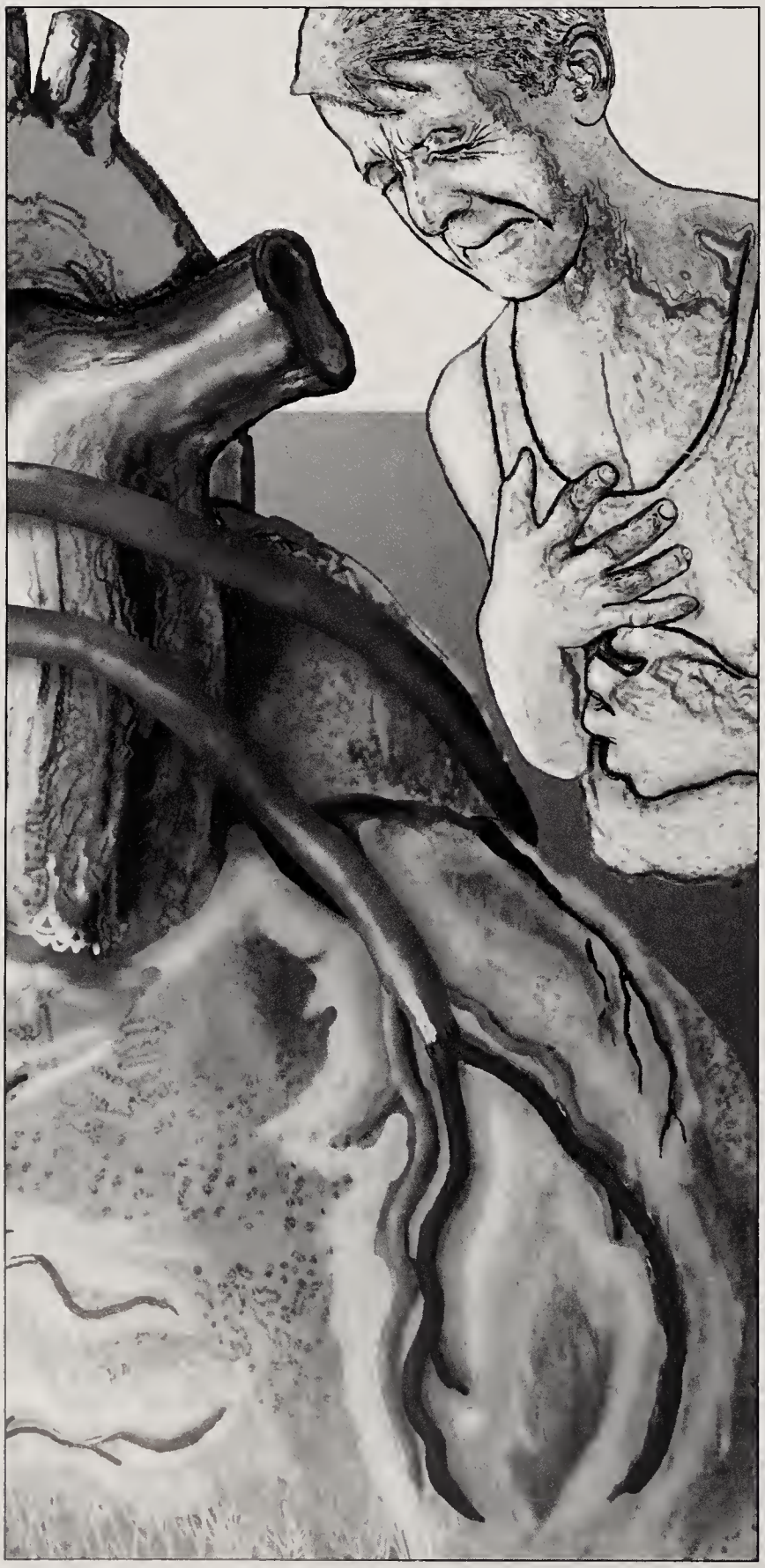

LAUREEN MAASKE

Abstract

Objective: To characterize the post-aortocoronary bypass patients admitted for coronary angiography for unstable coronary syndromes, the long-term therapy selected, and the outcomes of the intervention.

Design: A descriptive retrospective study

Setting: A university-affiliated tertiary care institution.

Patients: During the year of 1991, 129 patients with one previous aortocoronary bypass surgery who subsequently underwent coronary angiography for myocardial infarction or unstable angina were identified. Patients who had received coronary angioplasty, atherectomy, or stenting after bypass operation were not included in this study.

Methods: Information regarding initial aortocoronary bypass surgery, indications for cardiac catheterization, cardiovascular risk factors, ultimate treatment selected, and outcome at 1 year were abstracted from subjects' charts. Patients were followed for one year and outcomes during this period were recorded.

Main results: Seventy-six patients (59%) were treated with medical therapy, 28 patients (22%) with angioplasty, and 25 (19%) with repeat surgery. Patients' outcomes during their index admissions were as follows: A. medical therapy: 4 patients (5.3%) died from myocardial infarction, and 42 (55%) were discharged without complications; B. angioplasty: all except 2 attempts were successful; major procedural complications included non-fatal myocardial infarction in 1 patient (4%), and non-fatal ventricular arrhythmia in 1 patient (4%); two patients (7%) had reocclusion of the lesions prior to discharge; C. repeat surgery: there were no peri-procedural complications. All except one patient (96%) who died from myocardial infarction during the post-operative period, were discharged from the hospital. Other early complications included non-fatal myocardial infarction in 2 patients (8%), angina in 2 (8%), and non-fatal arrhythmias in 11 patients (44%).

Eighty-six patients (67%) were available for follow-up at 1 year. Of the patients who were treated medically, 3 patients (6.4%) had died, 14 (30%) had recurrent anginal episodes, and 5 (11%) required either angioplasty or bypass surgery. Of patients who initially received angioplasty, 15 patients (63%) had recurrent angina but there were no deaths within the first year. Repeat angioplasty was performed in 12 patients (50%), and 2 patients (6.3%) required repeat bypass surgery. No patients in the bypass surgery category died or required repeat surgery or angioplasty. Three of these patients (19%) had recurrent angina within the first year. Patients in this category also enjoyed a greater degree of symptomatic improvement of coronary artery disease.

Conclusions: Patients who had previous bypass surgery and subsequently presented with myocardial infarction were more likely treated with conservative medical therapy when compared to those who presented with unstable angina. Within one year of intervention, recurrent angina occurred more often with patients treated by angioplasty, less in those treated by medical therapy, and least in repeat bypass patients.

Key Words: Coronary artery bypass, myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty

Introduction

Since the advent of aortocoronary bypass surgery a quarter of a century ago, physicians have been dealing with increasing numbers of patients with previous coronary artery bypass grafting (CABG) seeking medical attention for symptoms of unstable angina or myocardial infarction. This group of patients represents a heterogeneous population in which the disease process may involve both native vessels and grafts, and in which myocardial damage may be more severe than in those without previous bypass surgery. Consequently, the natural history and the therapy of such patients may differ from that of patients who have not had previous CABG. Patients diagnosed with acute transmural myocardial infarction (MI) generally receive thrombolytic therapy at presentation. However, treatment decisions for patients who are not candidates for thrombolysis are often delayed until a better visualization of the coronary anatomy is obtained with angiography. Treatment of symptomatic post-CABG patients with medical therapy alone, percutaneous transluminal coronary angioplasty (PTCA) or repeat CABG has not been studied by randomized clinical trial. Although it was suspected that the majority of the post-CABG patients were being treated by medical therapy alone, the exact proportion receiving each of these treatment modalities was unknown.

We describe our experience with this group of patients at our institution. The objectives of this study were: 1. to have a better characterization of the post-CABG patients who received coronary angiography for symptomatic coronary artery disease; 2. to determine what long-term therapy was selected for these patients; and 3. to document the outcomes of each of the three treatment modalities.

Methods

Patients selection

All patients with previous CABG who underwent diagnostic coronary angiography at The Toronto Hospital (General Division) between January 1, 1991 and December 31, 1991, were identified. The Toronto Hospital is an university-affiliated tertiary care institution in Toronto, Ontario, Canada.

Patients were eligible for study if they had had either an acute myocardial infarct or unstable angina at the index admission for coronary angiography. Patients who had more than one previous CABG or PTCA after their first bypass surgery were excluded.

The diagnosis of acute myocardial infarct was based on clinical symptoms and on evidence of myocardial damage obtained from electrocardiograms and serum cardiac enzymes. Patients with unstable angina exhibited at least one of the following characteristics: new onset angina, rapidly progressing angina, angina at rest, angina refractory to medications, variant angina, acute coronary insufficiency with ECG changes but no significant enzyme changes, or post-MI angina.

Classification of the patients

After obtaining information from the heart catheterization, these patients were subsequently treated with one of the three aforementioned modalities. They were classified into three groups according to the treatment modality selected at the index admission:

Group A: These were patients who were considered to be best treated by medical therapy alone prior to their discharge – they were rejected for PTCA/redo-surgery either because of the high risk involvement based on the anatomy of the lesions, or because the benefit obtained would not outweigh the risk involved in the invasive procedures (ie. PTCA or bypass surgery).

Group B: Patients in this group were judged to be most suitable for PTCA based on the anatomy and the accessibility of the guide-wire to the lesion(s). They all consented for urgent bypass surgery in case of emergency complications during the procedure. Angiograms were taken immediately after the procedures and the residual stenoses were documented. A procedure was considered to be successful if the residual stenosis was less than 50% and the degree of stenosis was reduced by 40%. Patients might also receive other adjuvant therapies during the procedure, namely atherectomy and stenting.

Group C: These patients underwent urgent repeat bypass surgery at the index admissions.

Table 1

Characteristics	Myocardial infarction	Unstable angina
Number	27	102
Mean age (yr)	61.7	62.4
Male	25 (93%)	83 (81%)
Previous MI	15 (56%)	61 (60%)
Mean age of graft (yr)	6.9 +/- 4.1	6.7 +/- 4.0
Cigarette smoking (within the last 3 years)	20(74%)	60(59%)

Clinical characteristics of the patients (MI, myocardial infarction; yr, year)

To further characterize the lesions in the vessels, the native vessels and the vein grafts were divided into two and three anatomical sites, respectively. The native vessels were divided into proximal and distal, so that the section proximal to the posterolateral branch of right coronary artery (RCA) would be the proximal RCA, the section proximal to the first diagonal branch of left anterior descending artery (LAD) would be the proximal LAD, and the portion proximal to first obtuse marginal branch of circumflex artery (Cx) would be the proximal Cx. All the vein grafts were divided into proximal, body, and distal anastomoses, according to the sites where the grafts were attached to the native vessels.

Patients were followed for one year. Information was obtained by review of hospital charts, clinic charts, and sending out a questionnaire to each patient at the end of 1-year period. Information regarding symptomatology, additional investigations, and outcomes were requested in the questionnaire. The end-points of this study at 1 year included death, re-admission for symptomatic coronary artery disease, repeat CABG or PTCA, and improvement of symptoms of angina greater than two classes in the Canadian Cardiovascular Society Classification (CCS).

Results

Two hundred and twenty-one patients who had had previous CABG and received cardiac catheterization in 1991 were screened. Twenty-two patients had had more than one bypass surgery and another 23 patients had had angioplasty(ies) after their first bypass surgery but before 1991. Among the remaining 176 patients, 2 patients (1.1%) presented with arrhythmia, 4 patients presented with congestive heart failure with no evidence of myocardial injury at admission, 25 patients (14%) had chronic stable angina, and 16 patients were catheterized for other cardiac or non-cardiac related problems. All of these patients were excluded from the study. Thus, 129 patients were accepted for the study.

Of these 129 patients, 27 (21%) patients presented with acute myocardial infarction and 102 (79%) were diagnosed with unstable angina at the index admission. The clinical characteristics are reported in Table 1. Results from coronary angiography are shown in Table 2. Of note, 15% of all internal mammary grafts had greater than 69% stenosis, while an average of 30% to 50% of salphenous vein grafts in each patient had a similar degree of disease.

Patients were subsequently treated with medications alone, PTCA, or repeat CABG, based on the clinical decision of the attending physicians (Table 3). Seventy-six patients (59%), 28 patients (22%), and 25 patients (19%) were treated with medical therapy alone, PTCA, and repeat CABG, respectively. Of note, patients presenting with acute myocardial infarction were more likely treated with medical therapy alone, possibly because of irreversible myocardial damage.

Table 2

Variables	Myocardial infarction	Unstable angina
Mean LV function	grade 3	grade 2
Number of patients with left main artery s tenosis > 50%	3 (11%)	5 (5%)
Mean number of diseased native vessels with stenosis >69% per patient	2.4	2.3
Mean number ACB grafts per patient	2.8	2.9
Mean age of aortocoronary grafts (yr)	8.9	6.6
Mean number of diseased grafts with stenosis >69% per patient	1.4	1.0
Internal mammary artery	7 (26%)	32 (31%)
Internal mammary stenosis >69%	0	6

Coronary angiographic findings of the patients with previous ACB. Grade 1, EF>60%; grade 2, EF 40-60%; grade 3, EF 20-40%; grade 4, EF<20%. (ACB, aortocoronary bypass; EF, ejection fraction; LV, left ventricular; MI, myocardial infarction; yr, year)

Table 3

Treatment modality	Myocardial infarction	Unstable angina	Number of patients
Medical therapy	19(15%)	57(44%)	76(57%)
PTCA	4(3%)	24(19%)	28(22%)
Repeat ACB	4(3%)	21(16%)	25(19%)
Number of patients	27(21%)	102(79%)	129(100%)

Management of patients with previous ACB and recurrent coronary syndromes after coronary angiography.

Outcomes

Group A: Medical therapy

During their index admissions, 4 patients (5.4%) died from myocardial infarction, 1 patient suffered from a non-fatal MI, 21 patients (28%) had recurrent angina, and 8 patients (11%) had non-fatal ventricular arrhythmias. A comparison of their medications at admission and at discharges is shown in Table 4. Forty-two patients (57%) were discharged without any complications. Forty-seven patients (65%) were available at the end of one year and the outcomes are shown in Table 5.

Group B: PTCA

PTCA was used initially on 28 patients (22% of the 129 patients). Angioplasty of 27 lesions in 25 native vessels, and 14 lesions in 13 saphenous vein grafts was attempted (table 6). Twenty-two patients (79%) had only one dilatation attempt, four patients (14%) had two attempts, and 2 patients (7%) had 3 attempts. The mean stenosis of lesions was reduced from 80% to 24%. One attempt failed because the lesion was located just distal to the bifurcation of the circumflex artery from the left main coronary artery, which formed a sharp turn and was too difficult for the guiding wire to pass through. In the other attempt, reocclusion occurred at the dilated site shortly after the PTCA. All attempts performed on saphenous vein grafts achieved initial success. Adjuvant therapy was employed in some patients: three patients had coronary atherectomy, two patients had coronary stenting, and 1 patient had intra-aortic balloon pump. None received thrombolytic therapy.

Adverse outcomes of patients who received PTCA are shown in Table 5. All early complications were managed conservatively with medical therapy and all patients were discharged from the hospital. The 1-year follow-up result is shown in the same table.

Group C: Repeat CABG

Based on clinical factors including age, previous myocardial damage, age of the grafts, left ventricular function, and angiographic findings, 25 patients (19%) were selected to have repeat CABG. Twelve of these (48%) were done on emergency basis, and the rest were performed semi-urgently. A total of 53 saphenous vein grafts (3 to LAD, 12 to diagonal branches of LAD, 18 to obtuse marginal branches of Cx, and 20 to RCA) and 18 internal mammary arterial grafts (to LAD) were implanted. Each patient received an average of (2.8 $\pm$ 1.0) grafts. Complications during hospitalization are shown in Table 5. During the one-year follow-up period (table 5), three patients (19%) were re-hospitalized within an average of (7.1 $\pm$ 3.6) months for recurrent angina. All 3 patients were discharged without requiring any invasive therapy, and there were no deaths.

Discussion

Patients who have had previous aortocoronary bypass surgery and experience recurrent symptomatic coronary artery disease represent a distinct population from those patients who have not had previous bypass surgery. Decision-making regarding management of these patients is more complex, and the conventional guidelines[1] may not be suitable for this purpose. Symptoms may originate from progressively diseased native vessels, from stenosed vein grafts, or both. Management depends not only on the anatomy of the lesions, but also on the age of the grafts, size of the viable myocardium in jeopardy, left ventricular function, age of the patient, and many other clinical variables[2].

As the current medical literature provides little information about the management of this subset of patients, we report the clinical characteristics and the outcomes of one such group who were treated with medical therapy, PTCA, or CABG, at the discretion of their attending physicians. In this study, more than half of these patients were treated conservatively at their initial presentations, while one-fifth received coronary angioplasty, and slightly less than one-fifth of these patients were selected for repeat bypass surgery at the index admission. Patients who underwent conservative therapy had higher morbidity and mortality during the admission and within the following year. Patients who were diagnosed with myocardial infarction without evidence of ongoing ischemia were more often treated with conservative

Table 4

Medications	At admission	At discharge
Aspirin	47(62%)	43(60%)
Beta-blockers	31(41%)	39(54%)
Calcium-channel blockers	47(62%)	48(67%)
Nitrates	44(58%)	48(67%)
Diuretics	16(21%)	17(24%)
ACEI	16(21%)	22(31%)
Type I/III anti-arrhythmics	12(16%)	11(15%)
Anti-coagulants	11(14%)	9(13%)
Total number of patients	76(100%)	72(100%)

Patients treated with medical therapy alone: medications at the time of admission and discharge.

management. On the contrary, for patients presenting with unstable angina or with a large area of viable myocardium at risk for further damage, PTCA or repeat CABG were more often selected. While equal proportions of patients in PTCA group and medically-treated group gained significant symptomatic relief (defined as more than 2 levels of symptomatic improvement in CCS classification), bypass surgery was superior to these two modalities in terms of symptomatic improvement, frequency of need for repeat invasive therapeutic modality, and 1-year mortality in carefully selected candidates. Most of the patients in the PTCA group who experienced recurrent symptoms within one year were likely suffering from restenosis of the same lesion(s).

The mechanism of graft closure and the histopathology of graft lesions have been described in previous reports[3-6]. Internal mammary grafting provides superior long-term patency than the vein grafting[7-9], and maximal usage of internal mammary graft to bypass lesions in the left anterior descending artery would decrease the frequency of need for reoperation[2,7]. Our study showed that compared to saphenous vein grafts, a smaller proportion of internal mammary grafts were found to have stenosis in excess of

Table 5

	Medical therapy	PTCA	Repeat ACB
Early complications			
Death	4(5.3%)	0	1(4%)
Non-fatal MI	1(1.3%)	1(4%)	2(8%)
Non-fatal ventricular arrhythmias	8(11%)	1(4%)	11(44%)
Reocclusions	-	2(7%)	-
Aneurysm formation	-	1(4%)	-
Hematoma	-	3(11%)	-
Wound infection	-	-	3(12%)
Intra-aortic balloon pump	-	1(4%)	4(16%)
Urgent ACB surgery	-	0	-
Number of patients available for 1-year follow-up	47	24	16
Late outcomes			
Death	3(6.4%)	0	0
(Repeat) PTCA	3(6.4%)	12(50%)	0
Repeat ACB	2(4.3%)	2(8.3%)	0
Recurrent angina	14(30%)	15(63%)	3(19%)
Improvement with >2 CCS class	9(19%)	5(21%)	8(50%)

Early and late outcomes of patients who received medical therapy, angioplasty, and repeat ACB (CCS, Canadian Cardiovascular Society; LV, left ventricular; MI, myocardial infarction; yr, year;"-", not applicable)

Table 6

	A total of 41 lesions						
	27 lesions in 25 native vessels			4 lesions in 13 saphenous vein grafts			
	RCA	LAD	Cx	RCA	LAD	Diag	OM
Proximal	5	2	7	0	0	1	0
Mid-shaft	-	-	-	1	0	0	2
Distal	4	2	7	5	3	2	0

Location of lesions in PTCA group prior to coronary angioplasty. All except 2 attempts in native vessels gained initial success. (Cx, circumflex; LAD, left anterior descending artery; RCA, right coronary artery; "-", not applicable)

70%. Several hypotheses that explain the better patency of internal mammary grafting from pathophysiologic standpoint have been proposed[10-12]. Coronary-stent implantation has been proven by randomized trials to achieve better clinical and angiographic outcomes than standard coronary angioplasty of native vessels[13,14]. Its efficacy in treating diseased vein grafts as a sole therapeutic modality or as an adjunctive therapy to balloon angioplasty has not yet been shown. On the other hand, data comparing direct atherectomy with balloon angioplasty has not yet been published, although it is considered an effective adjunct after unsuccessful PTCA[15].

The decision to use PTCA or redo-bypass to treat patients with previous bypass grafts who later present with recurrent coronary syndromes depends on many clinical considerations[2]. The more important factors include the age of the grafts[16], left ventricular function, size of myocardium at risk[17], the general physical condition of the patient, and the location and extent of the lesions. Contrary to conclusions of a recent randomized trial comparing the efficacy of PTCA with CABG in treating coronary artery disease[18], the experience from our institution showed that the decision of surgery versus PTCA is usually dictated by clinical factors, as the clinical characteristics might be different between the two populations.

Angioplasty is an effective and a convenient way of managing discrete lesions and relieving patients' symptoms. It causes less short-term morbidity and reduces hospital days when compared to redo-bypass surgery. At our institution, the average success rate of PTCA was greater than 90%, and there was no significant difference in success rate between dilating a native artery or a vein graft. This result was comparable to those reported in the medical literature[19-21]. However, restenosis of the lesions represents a frequent problem, and because of this, more than fifty percent of the patients in this study group experienced recurrent anginal symptoms and required redo-PTCA or bypass surgery within months. It is possible that superior symptomatic results could have been obtained in these patients if CABG had been performed at their initial presentation. During this time of fiscal restraint, further economic analysis may provide a guideline for selecting treatment modalities when clinical considerations do not lean towards PTCA or bypass surgery in these patients.

One deficit of the study was the significant number of patients lost to the follow-up. None of these lost patients were deceased, according to the hospital registry. Missing data were mostly due to non-returned questionnaires.

Conclusions

Patients with previous aortocoronary bypass surgery and recurrent anginal symptoms represent a distinct population from those without previous bypass surgery. Management decisions are much more complex and should be individualized before a consensus guideline is available. In our patients, those with myocardial infarction were more likely treated with medical therapy than patients presenting with unstable angina, who were frequently treated more aggressively. Repeat CABG was a safe procedure in selected patients. It provided long-term relief of symptoms, especially using the internal mammary grafts which have a better cumulative patency rate than the saphenous vein grafts. Lower incidence of morbidity, involvement of controllable rather than serious complications, shorter hospital stay, and shorter recovery period, suggest angioplasty as an alternative to redo-bypass surgery in these patients. Restenosis, however, remained a problem as more than half of the patients had recurrent symptoms and required further invasive therapy (PTCA or CABG). This may contradict the belief held by many clinicians that the use of PTCA reduces costs in the long-term compared with bypass surgery. Further economic analysis comparing these two modalities may be useful for future decision-making.

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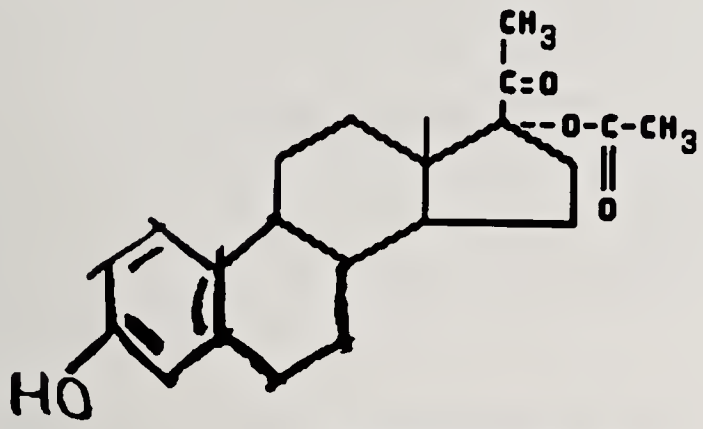

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The Prevention and Treatment of Nonsteroidal Anti-inflammatory Drug-induced Gastroduodenal Mucosal Injury

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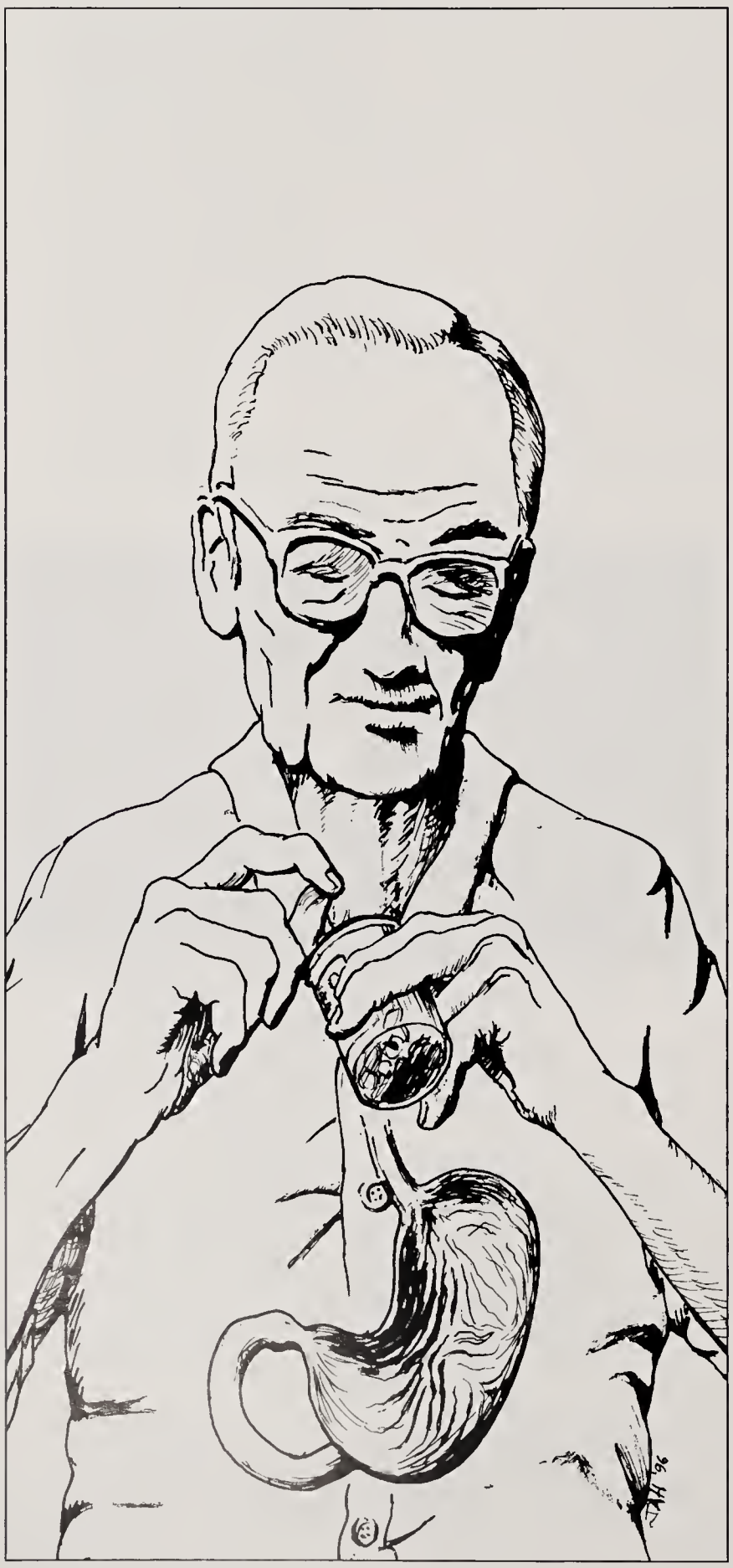


JOHN HIGGINSON

Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs in North America, but carry a significant risk of causing serious gastrointestinal injury, such as ulceration, bleeding, or perforation. This paper outlines the risk factors for NSAID-induced gastroduodenal mucosal injury, and reviews the methods available for their prevention and treatment. The evidence obtained from the results of recent trials, review articles and meta-analyses, is synthesized to construct a straightforward approach to the prevention and treatment of NSAID-induced gastroduodenal mucosal injury.

1. Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed by physicians as therapy for inflammatory and rheumatic diseases, such as rheumatoid arthritis and osteoarthritis. It is estimated that 30 000 000 people in the world use NSAIDs daily[1]. Unfortunately, a significant proportion of patients who take NSAIDs experience some gastrointestinal (GI) side effects. These are often mild, and consist mostly of dyspepsia, heartburn, and mild abdominal discomfort. However, NSAIDs may also cause more severe problems, including gastric and duodenal ulceration and gastrointestinal bleeding or perforation. The prevalence of ulcerations in NSAID users has been found to be 12-30% for the stomach (compared to 0.3% in the general population) and 2-19% in the duodenum (versus 1.4% in the general population)[2]. Moreover, a recent meta-analysis calculated that individuals who use NSAIDs have a risk of 2.74 times that of the general population for significant adverse gastrointestinal events (bleeding, perforation, event requiring hospitalization, or death)[3], with the risk averaging 1-2 per 1000 users per year[4] (ranging from 0.4/1000 in the young to 4/1000 in the elderly). NSAID-induced GI injury has been calculated to account for 42% of hospital admissions of patients with rheumatic disease, and one-third of the cost of treating rheumatic disease in the United States[5] (figures for Canada are not available).

Given that physicians often prescribe NSAIDs, and that these drugs carry a significant risk of severe gastrointestinal side effects, it is important for the physician to know how

best to prevent and treat NSAID-related gastroduodenal mucosal ulceration. The goal of this paper is to reach a conclusion about the role of different modalities in preventing and treating NSAID-induced ulcers, based on current scientific evidence. To answer this question, the results of recent published studies in the areas of risk factors for GI ulceration, prevention of ulceration, and treatment of ulceration will be reviewed. The evidence obtained from these studies will be combined with the opinion of experts in the area (as reflected in review articles) to construct a rational, evidence-based approach for the prevention and treatment of NSAID-induced ulcers.

2. Risk Factors for Complications of NSAID-associated Injury

Mild GI signs and symptoms have been shown to be poor predictors of NSAID-mediated injury. Although NSAID use often results in the experience of abdominal discomfort or dyspepsia, the presence of these symptoms correlate poorly with the presence of gastroduodenal mucosal injury. Studies have shown that approximately 40% of patients with endoscopic evidence of mucosal erosions are asymptomatic, and that up to 50% of patients with dyspepsia have normal appearing mucosa on endoscopic examination[6]. A study by Armstrong and Blower demonstrated that in patients hospitalized for GI haemorrhage who had been on NSAIDs, 58% had no prior GI symptoms[7]. It has been theorized that the analgesic effects of NSAIDs may account for the poor correlation of dyspepsia with ulceration.

Clearly, one cannot rely on patient-reported symptoms to herald the onset of NSAID-mediated mucosal injury. Therefore, it is important that the physician be aware of risk factors which identify the subsets of NSAID users who are at an especially high risk for developing NSAID-related complications. As will be discussed below, this knowledge may be used to decide which patients would benefit most from therapy aimed at preventing gastroduodenal ulcers.

Certain risk factors have been demonstrated in randomized controlled prospective trials to be highly significant in determining the risk of GI injury. These include:

(a) ***age*** Older people (>60 years old) are more likely to experience NSAID-associated injury of the gastroduodenal mucosa than younger individuals, and injuries are more likely to have a fatal outcome than in younger people[8]. A meta-analysis involving 16 studies showed that NSAID users over 60 years of age carried a relative risk of 5.5 for development of a serious GI complication, as compared to users under the age of 60[9]. The reason for the effect of age on risk for ulcer complications is unknown.

(b) ***prior history of ulcer or complications*** A history of prior ulcer or ulcer-related complications in persons who take NSAIDs carries a relative risk of 4.8 for serious GI complications over individuals with no such history who take NSAIDs[10].

(c) ***corticosteroid use*** One study calculated that the relative risk of GI complications in patients taking both corticosteroids and NSAIDs is up to 10.6 times the risk in those taking only NSAIDs[11]. Thus, the use of corticosteroids concommitantly with NSAIDs represents a high risk situation.

(d) ***NSAID dose*** A direct relationship has been demonstrated repeatedly between the NSAID dose and the risk of GI complications. For example, one study found that the relative risk of GI complications compared to controls was 2.8 for standard doses of NSAIDs versus 8.0 for higher doses[12].

Other factors are thought to be important in determining risk of GI complications in NSAID users, but their significance has not been conclusively demonstrated. These include:

(a) ***smoking*** Smoking is known to be a risk factor in the formation of peptic ulcers, but the meta-analysis mentioned above concluded that smoking has not been shown to increase the risk in NSAID users[13]. Therefore, one cannot say with certainty whether NSAID users who smoke represent a high risk group for NSAID-induced ulcers.

(b) ***alcohol*** A recent review concluded that there is insufficient evidence to show whether alcohol intake increases the risk for GI damage in NSAID users[14].

(c) ***anticoagulants*** No randomized controlled trials have shown an increased risk of ulcers or ulcer-related complications in NSAID users who also take anticoagulants (heparin or coumadin). However, a retrospective study showed a relative risk for haemorrhagic ulcer of 2.2 in NSAID users who also took anticoagulants as compared to NSAID users who did not take anticoagulants[15]. Consequently, it seems likely that use of anticoagulants along with NSAIDs places a patient at higher than average risk for ulcer complications, but further study is necessary to prove this relationship.

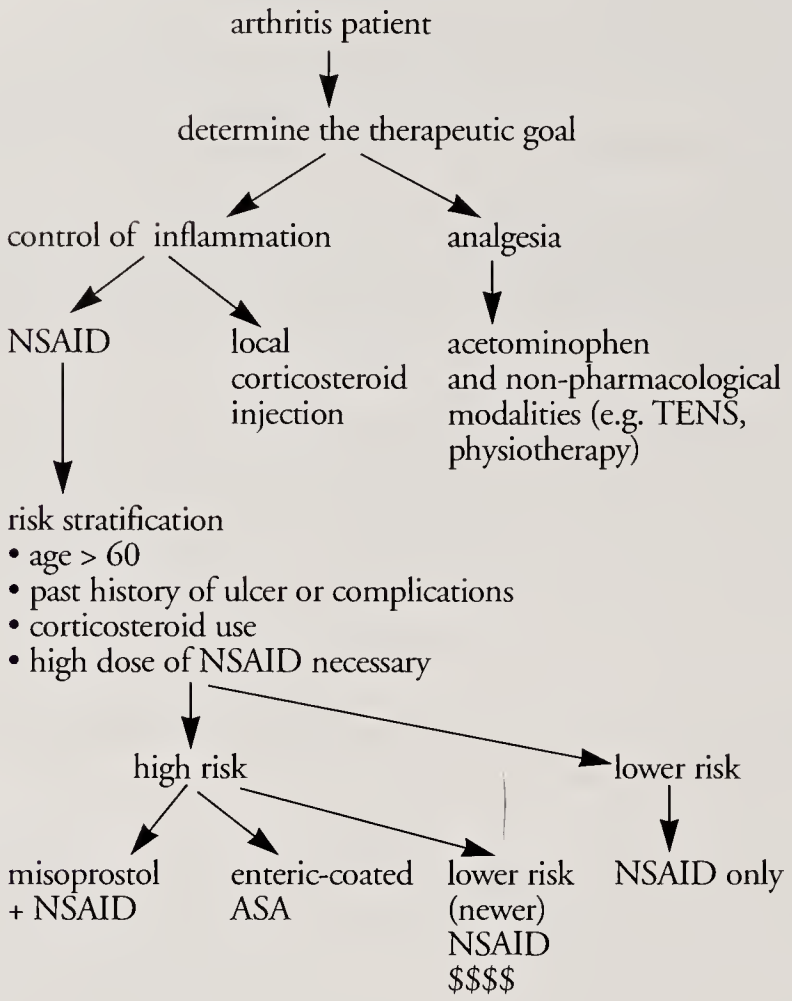
(d) ***Helicobacter pylori infection*** This bacteria is known to be a causative agent in the pathogenesis of gastroduodenal ulceration[16]. The relationship between *H. pylori* infection and NSAID use in the formation of ulcers, however, is unknown. Several studies have shown that infection with the bacteria neither influences the propensity of NSAIDs to produce ulcers nor does it affect the likelihood of occurrence of upper GI symptoms[17,18].

3. Prophylactic Therapy for NSAID-induced Gastroduodenal Injury

Having identified who is at the highest risk for NSAID-induced GI injury, the logical question to ask is whether it is possible to prevent such injury. Several methods to attempt to lessen the risk of injury have been studied.

(a) ***choice of NSAID*** The most effective strategy for preventing NSAID toxicity would be to avoid use of NSAIDs. Though this sounds overly simplistic, a recent randomized, double blind trial showed that acetaminophen (e.g. Tylenol) was as effective as ibuprofen (Advil) for the short term relief of osteoarthritic pain[19]. This indicates that NSAIDs may not always be necessary to achieve therapeutic goals, and that less damaging agents may be sufficient to fulfil the same role in some cases. Thus, before prescribing NSAIDs, the physician should consider whether it is the analgesic or antiin-

Figure 1
Appproach to ulcer prophylaxis in NSAID users



flammatory property of the drug which is desired in order to control symptoms.

The choice of NSAID may itself influence the likelihood of GI injury. Enteric coated aspirin has been demonstrated in endoscopic studies to cause significantly less topical gastric injury than uncoated aspirin, and thus, in theory, has a lower ulcerogenic potential[20]. Some of the more recently developed NSAIDs are thought to have lower rates of GI mucosal injury. Controlled trials of nambumetone (Relafen) have shown a much lower rate of GI toxicity with this drug than with other NSAIDs[21]. Singh et al. compared the relative toxicities of different NSAIDs and found that ASA and salsalate (Disalcid, a non-acetylated salicylate) were far less toxic to GI mucosa than other NSAIDs such as indomethacin (Indocid) and meclofenamate (Meclomen)[22]. Their study, however, did not control for varying drug dosages, so toxicity in the real world may differ from the toxicity reported in the study. One must also consider that newer NSAIDs tends to be far more expensive than older NSAIDs, and thus may not always be appropriate choices for all patients. The relative ulcerogenic potential of different NSAIDs is an emerging issue which represents an important area of study for the future.

(b) ***misoprostol*** Misoprostol (Cytotec) is a prostaglandin analog. Prostaglandins are polyunsaturated fatty acids derived from arachidonic acid in cell membranes by the actions of the enzymes phospholipase A_2 and cyclooxgenase (inhibition of the latter enzyme is the one of the mechanisms by which NSAIDs are believed to cause gastroduodenal injury). Prostaglandins reduce gastric acid secretion by inhibiting the formation of cyclic AMP (CAMP) within the cell[23]. Other actions of prostaglandins (the exact mechanisms are beyond the scope of this paper) help to protect the gastroduodenal mucosa[24], a phenomenon which has been called "cytoprotection" [25].

In a multicentre randomized controlled trial of patients with osteoarthritis, NSAID-induced gastric ulcerations developed in 21.7% of people receiving placebos, but in only 1.4% of the subjects who received misoprostol 200 mg four times per day along with an NSAID[26]. Similar results have been obtained in other randomized controlled studies[27]. Misoprostol has also proven to be effective in the prevention of duodenal ulcers - in one large trial, the incidence of duodenal ulceration after three months of NSAID use was 6.3% in the placebo group and 1% in the misoprostol group. Therefore, misoprostol may effectively prevent both gastric and duodenal mucosal injury in persons taking NSAIDs.

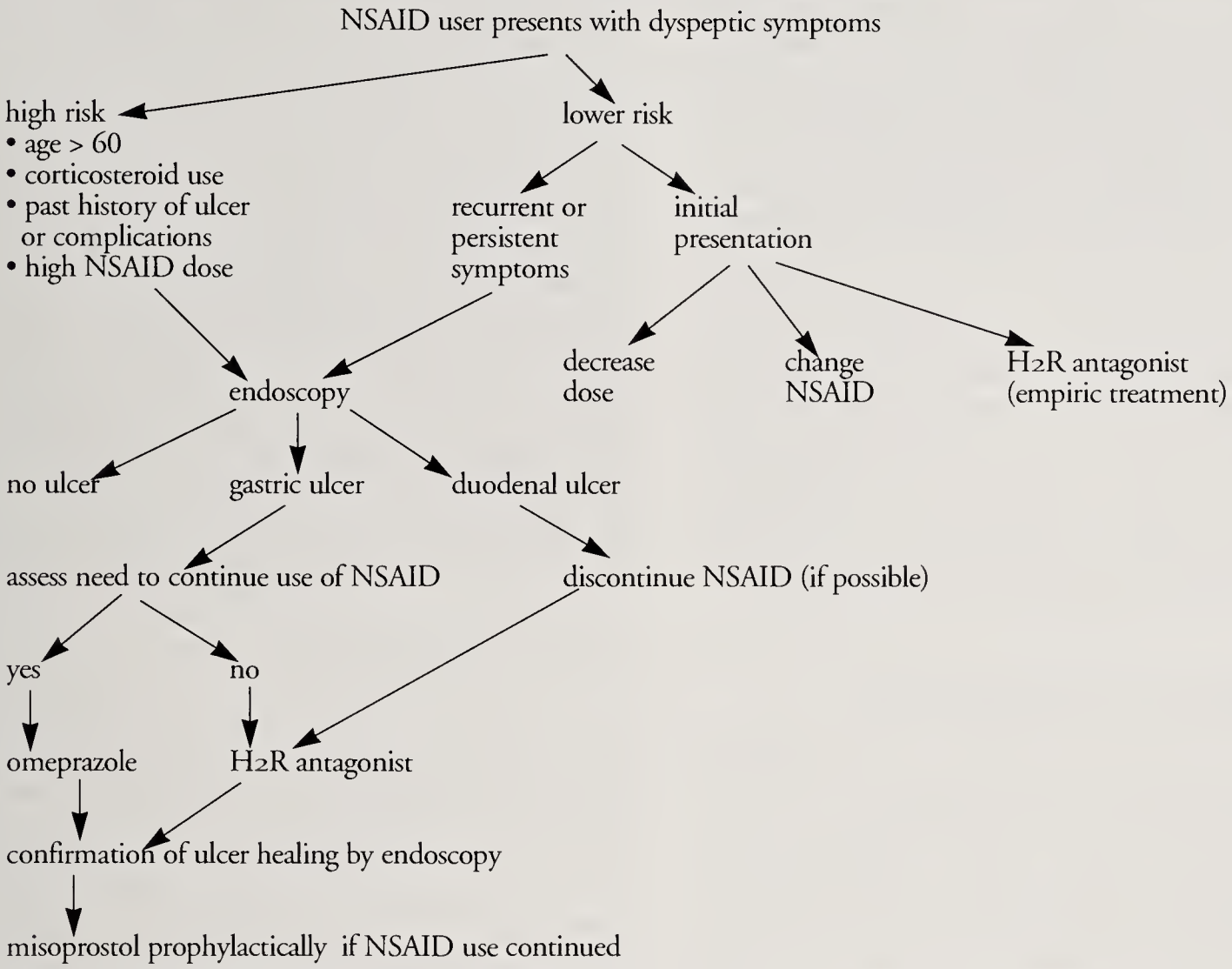
Misoprostol has also been shown to reduce the incidence of ulcer complications, such as perforation, gastric outlet obstruction and bleeding. A randomized placebo-controlled trial involving over 8000 patients with rheumatoid arthritis demonstrated a 40% reduction in the incidence of such complications in the misoprostol group[28]. This is evidence that the prevention of ulcers in NSAID users by the use of misoprostol will also prevent serious complications of ulcers. However, this study involved only rheumatoid arthritis patients; it is unclear whether these results can be generalized to other populations of patients who use NSAIDs.

(c) ***H_2-receptor antagonists*** These drugs block histamine receptors, thereby reducing histamine-induced gastric acid secretion. Two randomized, placebo controlled trials have compared the use of ranitidine (Zantac) to placebo in patients receiving NSAIDs[29,30]. In each study, an eight week course of ranitidine 150 mg bid was effective in preventing duodenal ulcer formation (rates of 0% and 1.5%, versus 8% for placebo), but was ineffective in preventing gastric ulcers. However, the relative efficacy of ranitidine with respect to misoprostol has not been studied. Based on its inability to prevent gastric ulcers in NSAID users, it seems prudent to avoid using ranitidine for ulcer prophylaxis.

(d) ***sucralfate*** Sucralfate (Sulcrate) is a locally acting agent which is believed to act by providing a physical barrier to injury and by stimulating the local defense mechanisms of the gastroduodenal mucosa[31]. A three month multi-centre randomized controlled trial in patients with rheumatoid arthritis comparing sucralfate with misoprostol revealed gastric ulcer rates of 16% in the sucralfate group and 1.6% in the misoprostol group[32]. Thus, sucralfate appears to be ineffective in the prevention of gastric ulceration with NSAID use. Its effects on duodenal ulcer prophylaxis are unknown.

(e) ***omeprazole*** Omeprazole (Losec) is a hydrogen ATPase inhibitor which directly blocks the secretion of H^+ into the gastric lumen, thereby reducing gastric acid secretion[33]. It has not been studied in any large scale trials in terms of its ability to prevent NSAID-induced GI injury. However, in a short (2 weeks), small (20 subjects) randomized controlled trial, rates of clinically significant gastrointestinal injury were

Figure 2
Approach to the NSAID user who presents with gastrointestinal symptoms



15% for gastric injury and 0% for duodenal injury in the subjects on omeprazole, versus 70% for gastric injury and 65% for duodenal injury for those on placebo[34]. The usefulness of this trial is severely limited by its small size, its short time span, and the fact that it was conducted in healthy volunteers (not in arthritis patients). Therefore, it is unclear whether the results can be extrapolated to the population of arthritis patients who are to be treated with NSAIDs; unfortunately, no other good studies are available which evaluate the efficacy of omeprazole in preventing ulceration in NSAID users[35].

4. Therapy of NSAID-induced Ulcerations

In the face of an ulcer produced by NSAID therapy, the best initial treatment would be to discontinue the offending agent. This may not always be realistic, however, because the patient may require the NSAID for the control of arthritic symptoms related to inflammation. Thus, the question that must be answered is whether it is possible to treat peptic ulcer disease without discontinuing NSAIDs, and if so, how best to accomplish this.

(a) ***H2-antagonists*** A randomized controlled trial has shown that cimetidine can promote the healing of up to 60% of NSAID-induced gastric ulcers within one month and up to 92% within three months, even while NSAID therapy is continued[36]. In another trial, duodenal ulcers had a 79% healing rate after three months of H2-antagonist treatment with continuation of NSAID therapy[37]. A study by Lancaster-Smith et al., however, suggested that when NSAID therapy is discontinued, ulcer healing proceeds at a faster rate. In this 8 week randomized controlled trial, healing rates for confirmed gastric ulcers were 63% in those who continued to take NSAIDs, versus 95% in those who stopped. The figures for duodenal ulcers were 84% and 100% for each of the above groups[38]. Thus H2-receptor antagonists appear to be useful agents in the treatment of NSAID induced ulcers; however, their efficacy is enhanced by the cessation of NSAID administration during ulcer treatment.

(b) ***misoprostol*** Misoprostol has not been as well studied as the H2-antagonists for the treatment of NSAID ulcers. One randomized placebo controlled 8-week trial in rheumatoid arthritis patients showed that misoprostol was superior to placebo in healing both gastric and duodenal ulcers (67% vs 26%)[39]. This study used a different endpoint than most other studies, however, in that ulcer healing was defined as improvement from a well defined ulcer to an erosion (rather than complete healing). No other studies have been published about the role of misoprostol in NSAID-induced ulcer therapy. Hence, the available data do not support the use of misoprostol as an ulcer-healing agent.

(c) ***omeprazole*** A multi-centre randomized controlled trial compared the efficacy of omeprazole at 40 mg and 20 mg

with ranitidine at 150 mg bid in patients with gastric ulcers who continued to receive NSAIDs during treatment. The healing rates at eight weeks were 95% for the omeprazole 40 mg group, 82% for the omeprazole 20 mg group, and 53% for the ranitidine group. Additionally, the rates of healing in the omeprazole groups were similar to the rates in a group of patients treated with ranitidine who discontinued their NSAID use. This suggests that it is not necessary to discontinue the use of NSAIDs when using omeprazole to treat gastric ulcers[40]. Unfortunately, the ability of omeprazole to heal NSAID-induced duodenal ulcers has not been well studied.

Although the optimal treatment of NSAID-induced ulcers is not yet certain, several principles can be set forth. Whenever possible, the NSAID should be discontinued. In light of the available evidence, omeprazole and H2-antagonists appear to be superior to misoprostol in healing gastroduodenal mucosal injuries. It seems likely that omeprazole provides superior results over the H2-antagonists in cases of gastric ulceration where the NSAID must be continued.

5. Discussion and Conclusions

NSAIDs play an important role in the treatment of various rheumatic diseases, but have the unfortunate side effect of causing severe gastrointestinal complications in some patients. Because of the large number of people who take NSAIDs, the aggregate cost of NSAID-related complications is very high, in terms of morbidity and health care dollars. Until NSAIDs are developed that have no GI side effects and are relatively inexpensive, the issue of NSAID-induced GI injury will continue to be important.

It would be useful to prevent the onset of gastroduodenal mucosal injury in NSAID users (see Figure 1). One way of achieving this goal is to avoid the use of NSAIDs altogether where possible, by using non-pharmacological means to control pain, such as physiotherapy. Another alternative is to achieve analgesia without control of inflammation, using acetominphen, which does not carry the risk of GI ulceration. One may also consider using one of the recently developed NSAIDs, such as nambumetone, which have been demonstrated to carry less risk for GI ulceration. However, the newer drugs are very expensive compared to older NSAIDs, so they may not be practical alternatives in these times of shrinking health care budgets. Of the available drugs which have been studied to prevent NSAID-induced GI injury, only misoprostol has been demonstrated to be effective in the prevention of both gastric and duodenal ulcers in randomized controlled trials. The H2-receptor antagonists have only been shown to be effective against duodenal ulcers, but not against gastric ulcers. Therefore, based on the available evidence, only misoprostol can be recommended for the prophylaxis of NSAID induced ulcers.

The final question that remains to be answered about misoprostol is whether the use of misoprostol to prevent gastroduodenal ulceration is a cost-effective approach. Misoprostol is not inexpensive (calls to several Toronto area pharmacies revealed that the monthly cost for misoprostol would be about $30 for 200 (μ bid, or $45 for 200 (μ tid, plus a dispensing fee of approximately $10). A recent meta-analysis of pre-1994 studies of the cost-effectiveness of misoprostol concluded that there was insufficient data to make a firm statement about the cost-effectiveness of the drug[41]. One of the issues raised in this meta-analysis was that it was unknown (at that time) whether misoprostol reduced the rate of ulcer complications (rather than simply ulcer occurence). This issue has recently been addressed in the MUCOSA trial (Misoprostol Ulcer Complication Outcomes Safety Assessment)[42]. This trial has demonstrated a 40% reduction in complications (GI bleeding, perforation, gastric outlet obstruction) in the misoprostol group as compared to the placebo group. These results allay the concern raised in the meta-analysis, and therefore suggest that a more current meta-analysis is necessary to re-examine the issue of cost-effectiveness of misoprostol prophylaxis. In contradistinction to the findings of the meta-analysis, the sole Canadian cost-effectiveness study calculated that misoprostol prophylaxis is cost-effective in high-risk subsets of NSAID users where the risk of ulcer-related complications (haemorrhage, perforation, hospitalization) is high (>1.2%).

These high risk groups (based on the relative risk obtained from studies and the reported incidence of complications in otherwise health NSAID users) are comprised of patients >60 years old, patients with a prior history of peptic ulcer disease, patients who use corticosteroids concomitantly, and patients who are on NSAIDs at a high dose. Based on the Canadian cost-effectiveness study by Gabriel et al., these subsets of users are likely to benefit in a cost-effective manner from the use of misoprostol prophylactically. It is unclear whether NSAID users who smoke cigarettes, drink alcohol, use anticoagulants, or are infected with *H. pylori* also represent high risk subsets of NSAID users, and whether they too might benefit from misoprostol prophylaxis.

If gastroduodenal mucosal injury is not prevented in patients taking NSAIDs, then treatment of the injury will have to be initiated (see Figure 2). The first problem in managing NSAID-induced ulceration is the identification of the patient who has developed an ulcer. As mentioned above, NSAID-induced ulcers may present asymptomatically, and not all NSAID users with dyspeptic symptoms will turn out to have an ulcer when investigated. One approach, proposed by Lichtenstein et al. (based on the risk groups defined above), is to limit diagnostic studies to low risk patients with persistent symptoms or high risk patients at the time of presentation with dyspeptic symptoms[43]. The approach to low risk patients at the time when they initially present with dyspeptic symptoms is to change to a different NSAID, reduce the dose of the current NSAID, or administer empiric therapy with H2-receptor antagonists. The efficacy and cost-effectiveness of this approach have not been studied.

As discussed above, once diagnosed, treatment of gastric ulcers caused by NSAIDs seems to be best accomplished by omeprazole if NSAID use is to be continued. If the NSAID is stopped, the less expensive H2-antagonists will suffice to heal the gastric ulcer, often within eight weeks. If the GI injury is a duodenal ulcer, every effort should be made to discontinue the NSAID; following this, treatment should be initiated with an H2-receptor antagonist (since omeprazole has not yet been demonstrated to be effective in the treatment of NSAID-induced duodenal ulcers where the NSAID is continued). After treatment of any ulcer caused

by NSAIDs, confirmation of healing by endoscopy is recommended. Once the ulcer is healed, the patient should be maintained on prophylactic misoprostol along with the NSAID, as the patient belongs to a high risk group for ulcer recurrence (now having a prior history of peptic ulcer).

Many issues remain to be studied in the future. The results of the MUCOSA trial, as discussed above, necessitate a re-examination of the issue of cost-effectiveness of misoprostol. Better estimates of the risk for adverse gastrointestinal events induced by NSAIDs in various subsets of NSAID users will facilitate more accurate cost-effectiveness analyses. The role of omeprazole in healing NSAID-induced duodenal ulcers needs to be studied, especially in cases where the NSAID will not be discontinued during ulcer therapy. Newer NSAIDs are emerging which purport to have fewer GI side effects; the role of these NSAIDs has yet to be defined and analyzed. As the exact mechanisms of NSAID-induced injury are elucidated in more detail, perhaps one day NSAIDs will be developed which avoid causing gastroduodenal mucosal damage altogether.

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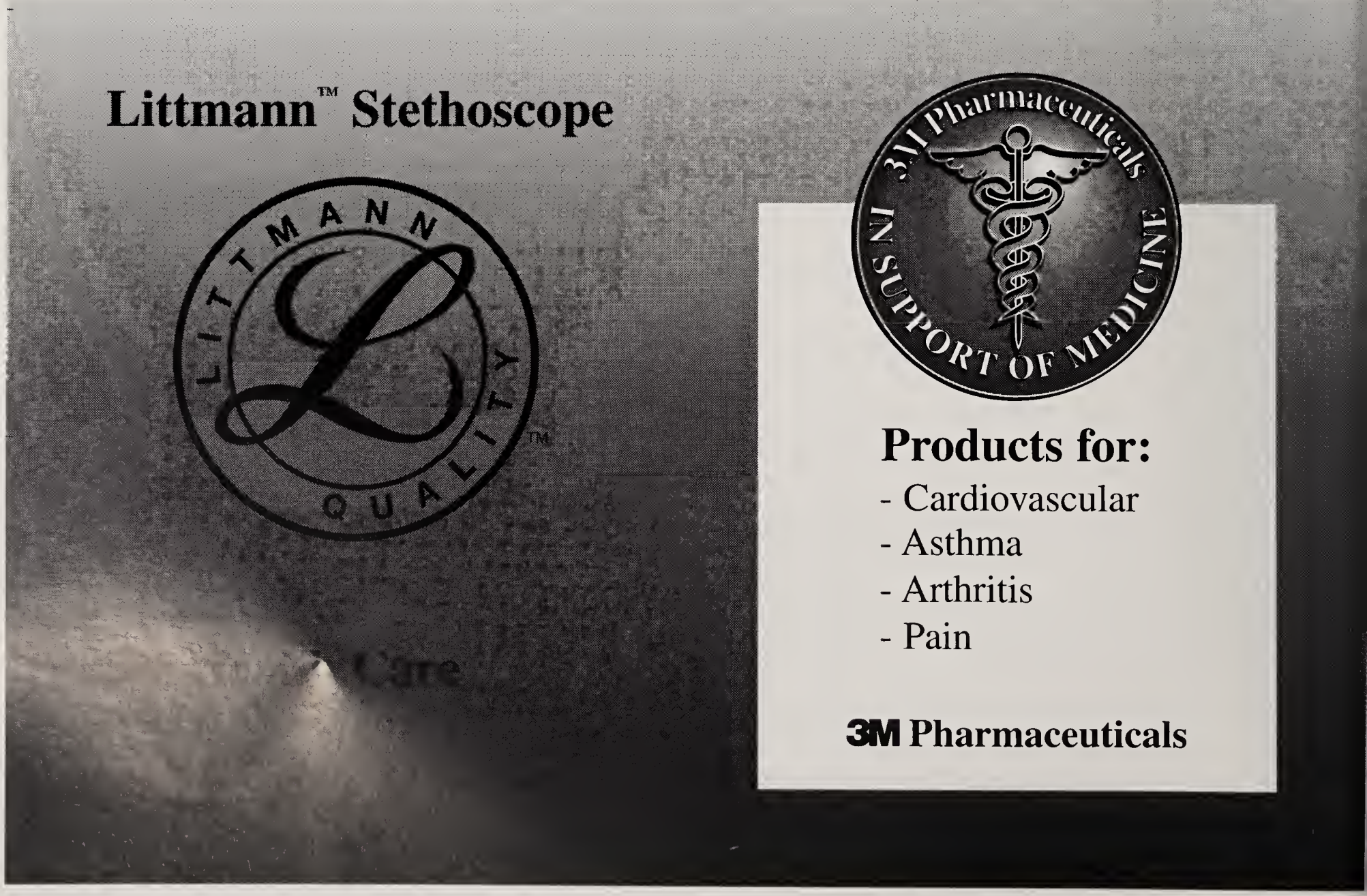

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Guarding The Genome: A Review of p53 Tumour Suppressor Gene

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Abbreviations

bp	-base pair
CAD	-Carbamoyl-P synthetase, aspartate transcarbamylase, dihydroorotase
Cdk	-Cyclin Dependent Kinase
CIP1	-Cyclin dependent kinase Inhibitor Protein
GADD45	-Growth Arrest and Differentiation Derived gene
MDM2	-Murine Double Minute gene
MDR1	-Multi-Drug Resistance gene
PALA	-N-(phosphonacetyl)-L-aspartate
PCNA	-Proliferating Cell Nuclear Antigen
TBP	-TATA box Binding Protein
WAF1	-Wild-type p53 activated fragment

Abstract

Scientists have shown that tumour suppressor genes are often inactivated in malignant cells, and the resulting loss of growth inhibition may play a role in cancer development and progression. Among tumour suppressor genes, the p53 gene has attracted most attention.The high incidence of p53 inactivation in cancer cells and its significant function in suppressing malignancy related phenotypes implies that loss of this gene represents a fundamental and crucial step in the pathogenesis of cancer. The function of p53 and its role in the development of malignancy has been extensively researched. It is now clear that p53 is induced by DNA damage, and its ability to suppress tumourgenesis and growth is described

as occurring through two predominant mechanisms; arrest of cell cycle and programmed cell death. p53 inhibits the progression of cells through the cell cycle in response to DNA damage, thus allowing cells time for DNA repair prior to cell division. Alternatively, p53 triggers apoptosis, programmed cell death, before damaged genetic material is passed on to progeny cells. In either case, p53 prevents the incorporation of damaged DNA, which has been shown to lead to genomic instability characteristic of malignant phenotypes. It is because of these properties that p53 is also known as the "guardian" of the genome. It is hoped that current studies into the mechanism of p53 inactivation in cancer and its regulatory functions in normal cells will produce results which will not only contribute to our knowledge of the pathogenesis of neoplasia but may also lead to advances in the treatment of cancer.

Introduction

The genetic paradigm which has dominated the field of cancer research for the last two decades stipulates that genetic alterations engender the phenotypes which confer malignant behaviour and drive the carcinogenic process. The first indication that alterations in specific genes are involved in the carcinogenesis process came from work in tumourgenic viruses where it was discovered that the activation of cellular genes by viral translocation resulted in a transformed phenotype. Since then, many proto-oncogenes and tumour suppressor genes have been identified, and much research has been focused on how these genes are altered in cancer, and on the mechanism involved in the transduction of their effects. The discovery that some oncogenes co-operate to elicit a tumourgenic phenotype, even if they could not do so individually, provided the first link between oncogenes and multi-step tumourgenesis. Neoplasia develops through a slow, multi-step process involving a sequential acquisition of selective phenotypic changes which allow cellular evolution towards increasing malignancy[1].

The existence of recessive mutations in cancer and tumour suppressor genes had been postulated from evidence in cell hybrid systems demonstrating that the replacement of a specific chromosome could suppress the tumourgenicity of some cancer cells, and the demonstration of allele loss at specific loci in many cancers. These genes are different from oncogenes in that their inactivation, rather than activation, is required for tumourgenesis. Several tumour suppressor genes have now been cloned and characterized. In human cancers, gene activation occurs by a variety of processes, most commonly mutation, allelic loss, chromosomal losses and rearrangements, binding to viral oncoproteins, and by other mechanisms. Some genes are only inactivated in specific types of cancers, but the p53 tumour suppressor gene has been shown to be frequently inactivated by mutation in a wide spectrum of cancers[2].

Structure of p53

The p53 gene is located on the short arm of chromosome 17 at the 17p13.1 locus and it is about 20 Kb in length, with 11 exons, the first of which is non-coding. The gene codes for a 53 KDa nuclear phosphoprotein which contains 393 amino acids. The NH_2 terminus of p53 is highly acidic[3] and the COOH terminus is rich in basic amino acid sequences containing three nuclear localization signals (NLS)[4]. The core region contains five evolutionary conserved regions involved in specific DNA binding[5]. Phosphorylation occurs at four sites in the NH_2 terminus end which are phosphorylated by putative kinases including the double stranded DNA protein kinase and casein kinase I. There are also two carboxyl-terminal sites that have been shown to be phosphorylated by cdc2, cdk2, and casein kinase II[6-8]. p53 forms homotetramers[9] and oligomerization is required for DNA binding and transcriptional activation[10]. An alpha-helix plus a basic region motif is a major determinant of the oligomerization domain in the C-terminus of p53[10, 11].

The structural elements present in many DNA binding proteins, such as zinc fingers, or helix-loop-helix motif, are not present in p53. Its structure has two antiparallel beta-sheets forming a beta sandwich that acts as a scaffold for supporting three loop based elements[12-14]. The first loop binds to the major groove of DNA, the second loop binds the minor groove, and the third loop acts against the second loop to stabilize it. There is a tetrahedrally coordinated zinc atom between the second and third loop holding them together[12].

Regulation of p53 Expression

Wild-type p53 has a short half-life of about 30 minutes[15-17]. The half-life of the protein could be altered in a number of ways including mutation[18], and binding to viral oncoproteins such as SV40 large.

T antigen and adenovirus protein[17, 19]. Interestingly, binding of p53 to E6, a human papilloma virus type 16 protein, leads to a decreased half-life for p53[20]. E6 leads to degradation of p53 and this involves the ubiquitin pathway as shown by identification of a ubiquitinated intermediate of the E6-p53 complex[20]. Proteins which become polyubiquitinated at a single site become targets for degradation[21]. It had been hypothesized that p53 may normally be degraded by ubiquitination and evidence of this has been reported showing that ubiquitination enzymes are involved in p53 degradation[22]. Further studies using a temperature sensitive mutant of the ubiquitination pathway reported accumulation of p53 when the ubiquitination pathway was perturbed[23].

There is very little known about the transcriptional regulation of p53, and most of the studies of p53 regulation have focused on post-transcriptional regulation. p53 is expressed at high levels in response to various conditions such as DNA damage in response to UV or ionizing radiation, but little is known about the signal transduction which occurs. The gene(s) responsible for Ataxia Telangiectasia (AT) may be involved in the signal transduction but are probably not directly upstream of p53 in the pathway. It has been suggested that p53 activates its own transcription by binding to its own promoter[24].

Accumulation of wild-type p53 protein in a cell could result from DNA damage[25] or viral oncoproteins[26, 27].

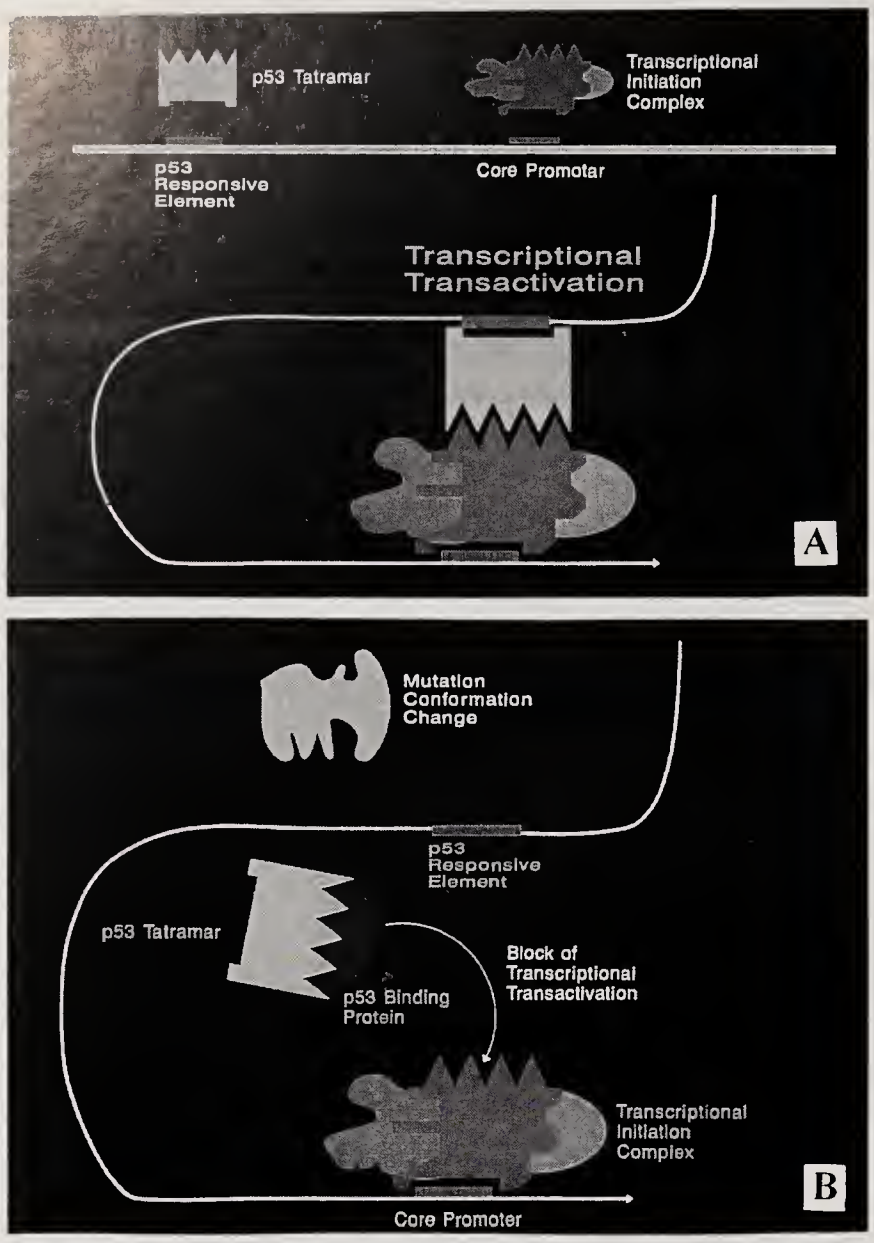

Figure 1: *Transcription transactivation by (a) normal p53 and (b) the modulation of this pathway when p53 has been altered.*

Missense mutations in p53 also lead to elevated levels of p53 protein, which could be detected by immunohistochemistry[15, 28, 29].

p53 Binding to DNA

The identification of p53 as a sequence specific DNA binding protein[30] first indicated that p53 may transcriptionally regulate specific genes. The consensus sequence for specific binding by wild-type p53 was described as two copies of a 10 bp motif which has been identified as the p53 responsive element[31]. The p53 responsive element is known to be present in the human ribosomal gene cluster (RGC)[30], murine muscle creatine kinase (MCK) gene[32], and others including the recently[33] discovered $p21^{CIP1/WAF1}$. Site specific binding of p53 to cellular DNA is inhibited by SV40 large T antigen and mutations[34].

X-ray crystallography analysis shows that the specific binding of p53 to the consensus site on DNA is mediated by direct contact between the p53 responsive element and specific residues. Interestingly, many of these residues are hot spots for mutation in many human cancers, indicating that the specific DNA binding transcriptional activity of those mutants would be diminished[12].

Transcriptional Activation by p53

The transactivation domain of p53 is in the NH_2-terminal 73 residues. When the 73 residues of the NH_2-terminal of p53 fuse to the DNA binding domain of yeast GAL4, it strongly activates transcription from the GAL4 promoter[35]. The binding of p53 to DNA specifically[30], in addition to the identification of a p53 responsive element in the MCK enhancer[32, 36] and in the ribosomal cluster gene region responsive element[30], suggests that specific p53 binding to DNA is required for transcriptional activation (Figure 1a). The identification of the p53 consensus binding site[31] and its presence in the promoter of various genes which are transcriptionally activated by p53 support this hypothesis. Unlike wild-type p53, mutant forms of p53 are not able to activate transcription *in vitro*[37-45] (Figure 1b). This suggests that loss of transcriptional activation by mutations in p53 leads to a selective advantage in the carcinogenic process. This is supported by the finding that specific transcriptional activation is essential for growth suppression by p53[46]. Until recently, the genes which were found to be transcriptionally activated by wild-type p53 did not have any direct association with growth suppression.

Recently, the $p21^{CIP1/WAF1}$ gene was discovered as a gene which is transcriptionally activated by p53[33], and which has a very strong association with growth suppression and cell-cycle arrest at the G1/S[33, 47]. $p21^{CIP1/WAF1}$ has a p53 responsive element in its promoter about 2.3 kb upstream of the start site which has the consensus sequence for p53 binding. Wild-type, but not mutant, p53[33] strongly activates transcription of $p21^{CIP1/WAF1}$, suggesting that tumours with mutant p53 would have lower expression of $p21^{CIP1/WAF1}$. Since p21 is involved in cell-cycle regulation and programmed cell death it is possible that p21 is a mediator of some of the effects of p53[48]. The levels of p21 are also elevated in response to DNA damage and it is involved in p53 mediated apoptosis further supporting its role in the p53-DNA damage response pathway[49]. This then provides a link between the requirement of p53 for transcriptional activation to cause growth arrest and inhibit cell-cycle progression[48].

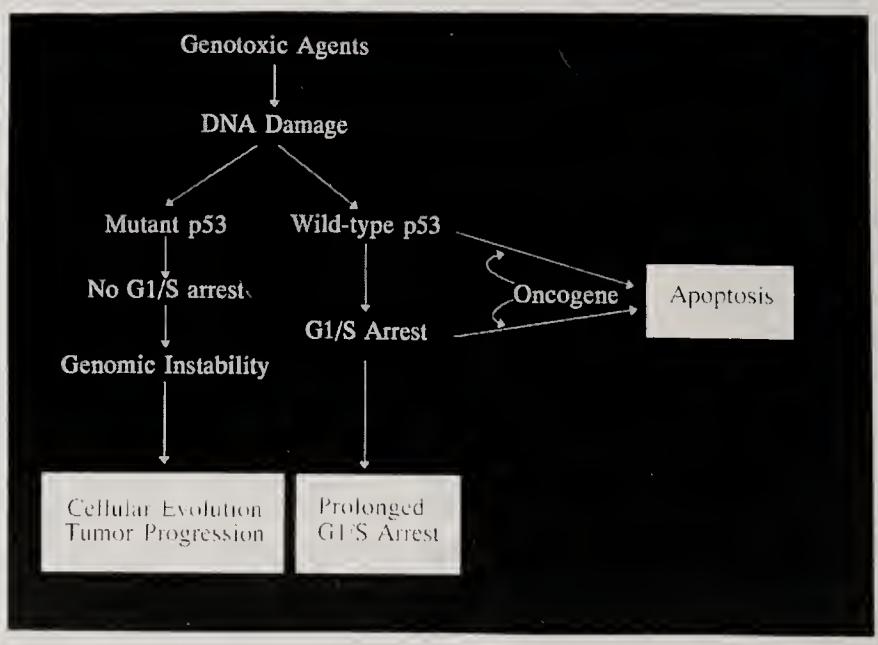

Figure 2: *Differences in the outcomes of DNA damage with mutant and wild-type p53.*

Transcriptional Inhibition

Binding of p53 to the TATA box binding protein (TBP) has been demonstrated and this may lead to either repression or activation of transcription, depending on the specific promoter[50-55]. Wild- type p53 has been shown to repress transcription from the promoter of several genes[56-61]. The exact mechanism of repression is not well understood but it has been suggested that binding of p53 to TBP may interfere with binding of the basal transcription factors to the TATA motif[62].

p53 Binding to Proteins

The p53 protein was first discovered because of its ability to bind to the large T antigen of the SV40 virus[26 27]. Binding of other viral oncoproteins such as the adenovirus E1B and the papilloma virus E6 have also been reported[63]. It is believed that these oncoproteins bind to p53 and inhibit its ability to suppress growth and cell division. This has been shown by the prevention of transcriptional activation by the large T antigen of SV40[34]. The advantage for the virus of having these p53 binding proteins is that the cellular proliferation that they require for replication is unabated by growth suppressors. Similar viral proteins bind and inactivate the RB protein, another growth suppressor[64].

Cellular proteins have also been identified to bind p53[6, 7, 65-68]. The murine double minute 2 (MDM2) protein was originally discovered as an amplified sequence in spontaneously transformed BALB/c 3T3 cells[70] and it was later discovered that MDM2 binds and interferes with the normal functioning of wild-type p53[40]. The MDM2 gene is in a region shown to be abnormal in many sarcomas, and its amplification has been observed in bone and soft tissue sarcomas[72]. MDM2 could inhibit p53 mediated transcriptional function[40] by forming complexes with p53[73], thereby concealing its transcriptional activation domain[41]. The loss of the tumour suppression function of wild-type p53 occurs when there is over-expression of MDM2[74]. p53 binds to a p53 responsive DNA sequence of the MDM2 gene leading to increased normal endogenous MDM2 expression[75]. The MDM2 gene contains a second internal promoter which is responsive to p53 and gives rise to MDM2 peptides which are incapable of binding p53. Altering the amount of p53 allows for the selective production of different MDM2. Hence, p53 modulates the production of MDM2 peptides through the activation of this internal promoter[76]. It has been suggested that p53 and MDM2 are in an auto-regulatory feedback loop where p53 transcriptionally activates MDM2 and MDM2 results in functional repression of p53[37]. Over-expression of MDM2 was also shown to inhibit the cell-cycle regulation function of p53 in the response to the DNA damage pathway[77]. The amplification of MDM2 may be an important mechanism by which sarcomas overcome the suppression effects of p53. However, there are some sarcomas that do not contain MDM2 in their amplicons, suggesting the possibility of additional genes driving the amplification[71, 78].

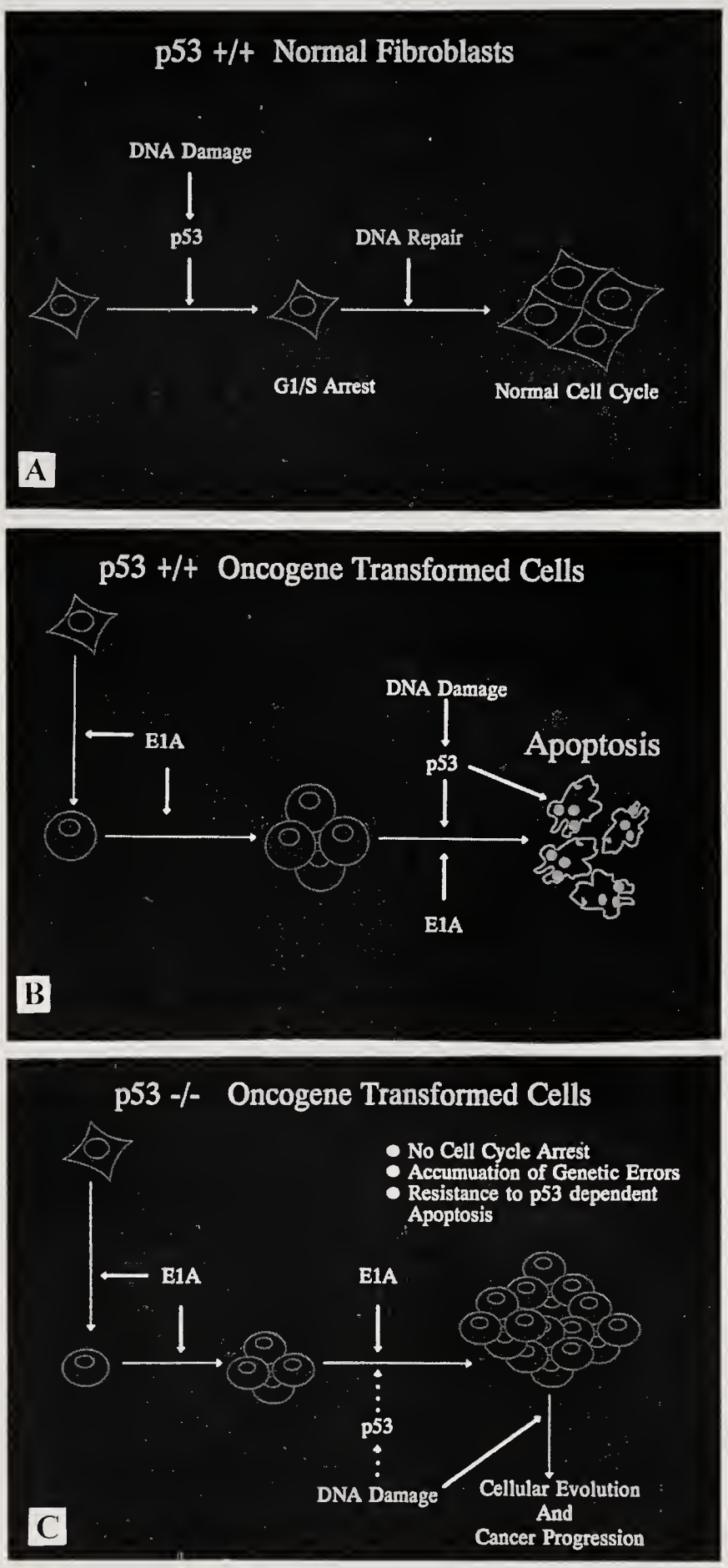

Figure 3: *Pathway of response to DNA damage in (a) normal cells with wild-type p53, (b) oncogene (E1A) transformed cells with wild-type p53, and (c) oncogene (E1A) transformed cells with mutant p53.*

p53-Dependent DNA Damage Response Pathway

The first indication of the involvement of p53 in the cellular response to DNA damage was stimulation of p53 expression after UV irradiation of non-transformed mouse cells[79]. A temporal association was later observed between levels of p53 and G1 arrest[25]. These findings were corroborated by other studies showing that DNA damaging agents cause

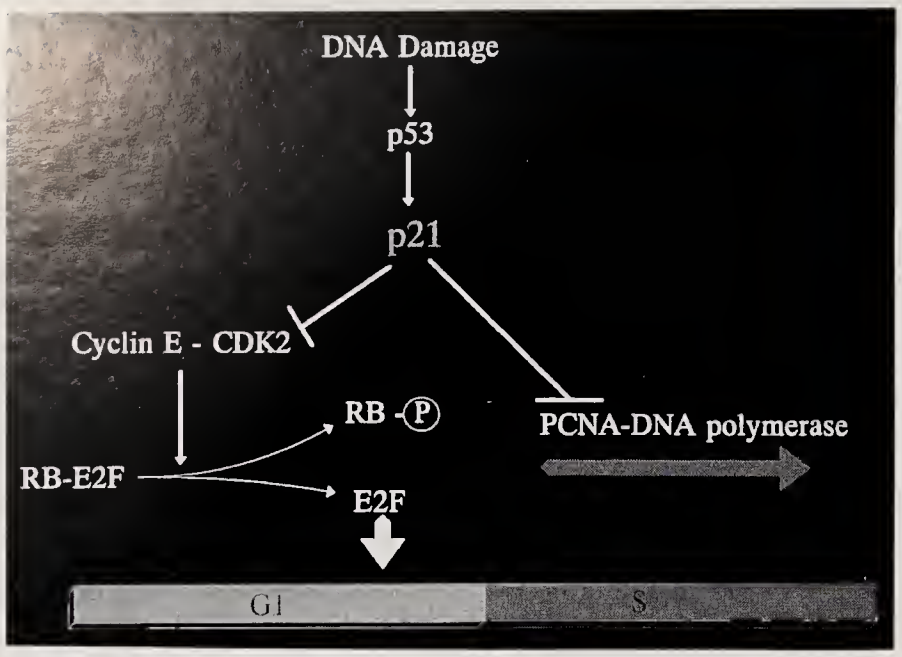

Figure 4: *Cell-cycle arrest by p21.*

growth arrest by inducing p53 which regulates the G1/S checkpoint[80-82]. The exact mechanism by which DNA damaging agents cause increases in p53 expression is not well understood, however, it has been postulated that DNA strand breaks are the stimuli which trigger the p53-response[83] (Figure 2). The pathway was partially delineated by the observation that the pathway is defective in cells from patients with Ataxia-Telangiectasia[84]. In the cells of these patients, p53 is not induced by DNA damage indicating that the gene(s) responsible for AT is upstream of p53[84].

p53 Checkpoint Regulation and Genomic Instability

The role of the p53 dependent DNA damage response pathway in carcinogenesis had been postulated to involve prevention of the accumulation of genetic errors by stopping DNA replication long enough for the cell to repair the damage. In this way p53 acts as a "guardian of the genome", by regulating the G1/S checkpoint and preventing the genetic instability which might ensue if DNA damage were allowed to cause errors to be incorporated through DNA replication[85, 86]. Evidence that loss of p53 function could result in genetic instability has come from studies showing that mutations in p53 result in an increased rate of gene amplification[87, 88]. The outcome of these studies suggest that the loss of p53 function, which leads to loss of the G1/S checkpoint, cause genomic instability and a loss of genetic integrity, ultimately allowing amplification to occur[87, 88]. Aneuploidy and abnormalities of the genome are hallmarks of cancer cells. One implication of the defects in cell-cycle checkpoints is that they are a mechanism by which cancer cells achieve genomic instability[89]. The increased plasticity which results from genomic instability could then drive the cellular evolution of neoplastic cells by allowing them to acquire selective genetic changes. The components of cell-cycle control and the mechanisms of checkpoint regulation are beginning to be defined, and this may allow insight into how cancer cells evade these controls. The p53 gene prevents genomic instability in the presence of DNA damage by regulating the G1/S checkpoint, making it an important component for the cell's ability to preserve genomic integrity, and a target for inactivation leading to neoplasia.

p53-Dependent Apoptosis

Apoptosis is a form of cell death which is characterized by cell shrinkage, chromatin condensation and intra-nucleosomal degradation of DNA[90]. The first study linking p53 to apoptosis[91] demonstrated that wild-type p53 induces apoptosis of myeloid leukaemic cells. Subsequent studies showed that p53 is involved in radiation induced apoptosis of thymocytes[92, 93]. p53 also triggers apoptosis in cells transformed with the viral oncogene E1A, presumably due to induction of proliferation by E1A being incompatible with induction of growth arrest by p53[94-96] (Figure 3). EIB inhibits p53 dependent apoptosis in E1A transformed cells by inhibiting p53 directly[9]. E1A sensitizes fibroblasts, induced by various DNA damaging agents in the presence of wild-type p53, to apoptosis. However, p53 deficient cells are resistant to apoptosis by these agents[97]. The implications of this is that loss of p53-mediated apoptosis represents a novel form of tumour cell resistance to chemotherapy and radiation therapy which is acquired by loss of p53 function[97]. In concordance with the above finding, replacing wild-type p53 in human lung cancer spheroids using a viral expression vector resulted in growth suppression by activating apoptosis[98]. The mechanism by which p53-dependent apoptosis is induced is not known but recent findings suggest that it does not involve transcriptional activation or transcriptional repression[99]. Different hypotheses have been formulated to explain the induction of p53 dependent apoptosis, however, the most favoured explanation is that p53 affects DNA repair directly or represses proteins required for cell survival[100]. It has been postulated that p53 arrests cells at the G1/S checkpoint in response to DNA damage, and allows enough time for the genetic changes to be repaired before DNA replication. However, if the DNA damage can not be repaired, then p53 triggers apoptosis[85]. Alternatively, p53 may cause apoptosis when there is unabated cell proliferation as caused by growth stimuli from inappropriate expression or activation of various oncogenes.

p21$^{CIP1/WAF1}$: A Mediator of Many of p53's Effects

Until recently, there was no clear connection between p53 and the cell-cycle. Several investigators isolated and characterized a p53-regulated inhibitor of cyclin-dependent kinases (cdk) which is both transcriptionally activated by p53 and has the ability to arrest the cell-cycle by binding to and inhibiting various G1 cyclin-dependent kinases (cdk)[33, 47, 101, 102]. p21$^{CIP1/WAF1}$ was originally isolated as WAF1 (wild-type p53 activated fragment 1), a gene which is induced by MDM2 but not mutant p53, and still retains the ability to act as a tumour suppressor[33]. p53 activation was shown to occur through a p53 binding site 2.4 kb upstream in the WAF promoter[33]. Introduction of WAF1 cDNA into various human tumour cells created a suppression of growth, but when a mutation was introduced in WAF1, creating a stop codon at residue 222, it did not result in any significant growth suppression[33].

p21$^{CIP1/WAF1}$, also known as cdk-interacting protein (CIP1), was independently isolated because of its ability to bind to Cdk[47]. Cdks interact with cyclins, which are only expressed at specific times during the cell-cycle, forming an active kinase enzyme complex which phosphorylates various down stream cell-cycle regulating proteins, and this drives the cell through the cell-cycle[103]. One regulatory protein which is phosphorylated by the cdk-cyclin kinase complexes is the Rb protein which usually binds and inactivates E2F, a transcription factor that is involved in progression of the cell-cycle. The phosphorylation of RB releases E2F and results in activation of the transcription of genes needed for entry into S-phase. CIP1 binds tightly to cdk and inhibits the kinase activity of the cdk-cyclin complex leading to cell-cycle arrest[47]. Since elevated levels of wild-type p53 also lead to cell-cycle arrest and p53 induces expression of p21$^{CIP1/WAF1}$, an inhibitor of the cell-cycle, it is likely that it is a mediator of p53's effects on G1 arrest of the cell-cycle[104].

p21$^{CIP1/WAF1}$ has also been identified as the p21 subunit of the quaternary complex containing a cyclin, a corresponding cdk, the proliferating cell nuclear antigen (PCNA) and p21[101]. Interestingly, p21 and PCNA are missing from this complex in certain tumours studies indicate that p21$^{CIP1/WAF1}$ is a universal inhibitor of G1 cyclin-cdk complexes[101]. This may be an over-simplification as p21 is a component of the quaternary cdk complex in normally dividing cells. Paradoxically, given that p21 should inhibit the activity of the kinase complex and prevent progression through the cell-cycle in normal cells. The effects of p21$^{CIP1/WAF1}$ on the kinase activity of the complex turn out to be more subtle, and a cdk complex containing p21 could exist in both the active and inactive states[105]. Cancer cells which lack p53 function could have as much as a 50 fold decrease in p21$^{CIP1/WAF1}$ levels and the lack of cdk-cyclin complex inhibition could result in unabated cell division[105]. p21$^{CIP1/WAF1}$ has been shown to be involved in p53-induced growth arrest at the G1/S checkpoint through inhibition of cdk-cyclin complex kinase activities. p21$^{CIP1/WAF1}$ could also control DNA replication by interacting with PCNA[106]. This would represent a second mechanism of growth arrest which would act after a cell has already passed the G1/S checkpoint by blocking the ability of PCNA to activate the main replicative DNA polymerase[106] (Figure 4).

The implications of p21$^{CIP1/WAF1}$'s involvement in cancer are numerous. To date, mutations in the p53 gene of neoplastic cells are observed more frequently than in any other cancer genes analyzed. Since wild-type p53 can induce expression, but mutated p53 can not, it is possible that p53 mutations are associated with a loss of p21$^{CIP1/WAF1}$ induction in tumour cells. This could lead to a subsequent increase in G1 cyclin-cdk kinase activity with the consequence of increased proliferation and loss of cell-cycle checkpoints. In fact, studies confirmed that p21$^{CIP1/WAF1}$ mRNA levels are lower in human breast cancer tumours which contain mutated p53 as compared to tumours where there was only wild-type p53[107]. This supports the hypothesis that at least some effects of p53 mutations observed in cancer cells, such as loss of cell-cycle checkpoints, loss of tumour suppression, and loss of p53 dependent apoptosis result from a subsequent reduction in p21$^{CIP1/WAF1}$ mRNA expression. It has been demonstrated that p21$^{CIP1/WAF1}$ is induced in p53-mediated G1/S arrest and apoptosis in response to DNA damage[49, 108]. In addition, p21$^{CIP1/WAF1}$ mRNA levels were shown to rise 10- to 20-fold during cellular senescence[102]. It is conceivable that loss of p21$^{CIP1/WAF1}$ induction or loss of its function may lead to a loss of senescence which could lead to neoplastic development.

Germ-Line p53 Mutations

Germ line p53 mutations were discovered to occur in Li-Fraumeni syndrome (LFS) which is a familial syndrome of sarcomas, breast cancer and other malignancies[109-111]. The transmission of the p53 mutations parallels a very high probability of developing early tumours in those family members. The constitutive cells of afflicted family members are heterozygous for p53 mutations, but the tumours have often lost the wild-type allele[109]. The association of p53 germ-line mutations with classic Li- Fraumeni families has been extensively documented[112-114]. p53 germ-line mutations have also been reported to occur in patients showing a second malignancy[115-117]. Since one of the major types of cancers observed with germ-line p53 mutations is sarcoma, it seems that p53 may play an important role in this type of tumour. Another implication is that some of the patients who have sarcomas may also have germ-line mutations. A subsequent study validated this hypothesis in patients either with or without family history of cancer[118]. Studies in humans have all suggested that patients with germ-line mutations in the p53 gene have a higher risk of developing various malignancies, especially sarcomas and this was also observed in transgenic animal studies using transgenic mice with a mutant p53 gene[119] and with null mutations in the endogenous p53 gene created by gene targeting and homologous recombination[120]. In this study, the mice were reported to have had a very high incidence of various cancers including mostly lymphomas and osteosarcomas.

Association between p53 Status and Clinical Outcome

Some correlations between p53 immunostaining and soft tissue sarcomas of high grade have been observed, and patients with high levels of nuclear p53 protein in more than 20% of the tumour cells tend to have reduced survival[121]. The analysis of p53 by immunohistochemistry alone, however, is not sufficient to assess the contribution of mutations in p53 to clinical outcome since mutations usually do not correlate with immunostaining. Although there is some association between clinical outcome and p53 immunostaining, the effect of mutations which do not lead to increased immunostaining, such as nonsense mutations, have been neglected. In general, expression of high levels of p53 protein is a significant predictor of a shorter patient survival time in various malignancies, including breast[122-124], colorectal[125, 126], lung[127, 128], gastric[125, 129], and brain tumours[129]. Only missense mutations lead to positive immunostaining, and thus, the ability of immunostaining to represent tumours with p53 mutations depends on the proportion of mutations which have mis-

sense mutations. In some types of cancer, nonsense p53 mutations which are not detected by immunohistochemistry account for about half the mutations observed. These would appear negative by immunohistochemistry. Also, false positive could occur if there is no mutation but p53 protein is at higher levels for some other reason. In some of the studies cited above, tumours which apparently had wild-type p53 but in addition also had high levels of protein did contribute to the group with poor prognosis. These samples may have p53 mutations, but are missed by DNA analysis, or the over-expression of p53 may indicate binding and inactivation by amplified MDM2. To accurately assess the effect of p53 mutations on clinical outcome, a combination of both DNA analysis and immunohistochemistry needs to be used in the analysis.

Concluding Remarks

The nature, spectrum and location of mutations found in the p53 tumour suppressor gene are very diverse[131], and their effects have been studied very extensively, resulting in an unprecedented amount of information on mutations in this gene. p53 was originally discovered as a protein which associates with the large T antigen of SV40[26, 27]. The p53 tumour suppressor gene was originally thought to be a dominant oncogene, but later it was discovered that the mutant forms of p53 which had transforming abilities acted in *trans* to inactivate wild-type p53[64]. Much of the early work on p53 focused on the transforming ability of p53 with a variety of oncogenes. These studies established much of the current knowledge about the relationship between proliferation and growth suppression in cancer cells, and the role that p53 has in this balance.

Unfortunately, advances have not been made in understanding the role of p53 function in cancer development. Many studies have shown that p53 mutations occur with varying frequencies and spectrums in different types of human tumours, but the biological basis for these differences still remains unclear. The studies that have examined the relationship between p53 mutations in human cancers, the malignant behaviour of the cancer, and the clinical outcome which it engenders have shown that p53 mutations do affect the malignancy of specific types of cancers. This association needs to be explored in a more comprehensive way with larger groups of patients for each type of cancer in order to assess the differences between types of cancers, and the biological basis for this association.

Clinical experiments are in progress looking at the effects of stably and functionally delivered genes by retroviral vectors into patients with neoplastic diseases[132]. As p53 inactivation has been identified as an important genetic event in the pathogenesis of Li-Fraumeni syndrome, colorectal adenocarcinoma, glioblastomas, breast cancer, sarcoma, liver cancer, and lung cancer[133-137], it is not surprising that investigations introducing p53 into p53 mutant or deleted cells have generated much interest[138]. To date, studies in experimental animal models have reported positive findings with p53 gene therapy in prostate cancer[139], 9L glioma[140], squamous cell carcinoma of the head and neck[141], breast cancer[142], and lung cancer[143]. With the advent of further improvements in technology and a better understanding of the molecular basis of cancer, gene therapy may eventually complement conventional cancer treatment.

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Reducing Noise In Functional MRI By Aligning Images Prior To Brain Activation Mapping

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Abstract

Functional magnetic resonance imaging (fMRI) is a novel approach to mapping brain activity. It relies on small differences between magnetic resonance images taken with a stimulus present (group 1) and with the stimulus absent (group 2). Because brain activation changes the images so subtly, multiple magnetic resonance images must be acquired to show any statistically significant differences. Since multiple images are required, the subject must remain motionless in the magnetic resonance imager for over thirty minutes. Any movement during this time causes the images in group 1 and group 2 to be misaligned. We questioned whether correcting the misalignment prior to statistical comparison would improve the quality of the functional magnetic resonance (fmr) image.

We collected multiple images that had been processed to create fmr images and displayed them in rapid sequential order (a movie loop). The movie loop displayed observable changes in head position between the images. Differences between the images were then quantified supporting the movement observed in the animation.

These images were processed resulting in a brain activation map obscured by noise. Our group had previously developed and tested a computer automated algorithm which we employed to align the collected images. The corrected images were processed resulting in brain activation maps with markedly reduced noise, confirming that aligning images prior to processing was worthwhile.

To further investigate the effects of misalignment, we collected a series of images that had been processed to create an fmr image that accurately demonstrated brain activation. We randomly misaligned these images using a computer-automated algorithm, and created an fmr image from the resulting misaligned images. This fmr image showed no areas of activation. When the computer algorithm was used to realign the images, the resulting fmr image showed the same area of activation as the original. From this we concluded that misalignment between images reduces the ability of fMRI to detect areas of brain activation. Our studies suggest that aligning images by a computer automated algorithm produces fmr images which better represent stimulus induced brain activation.

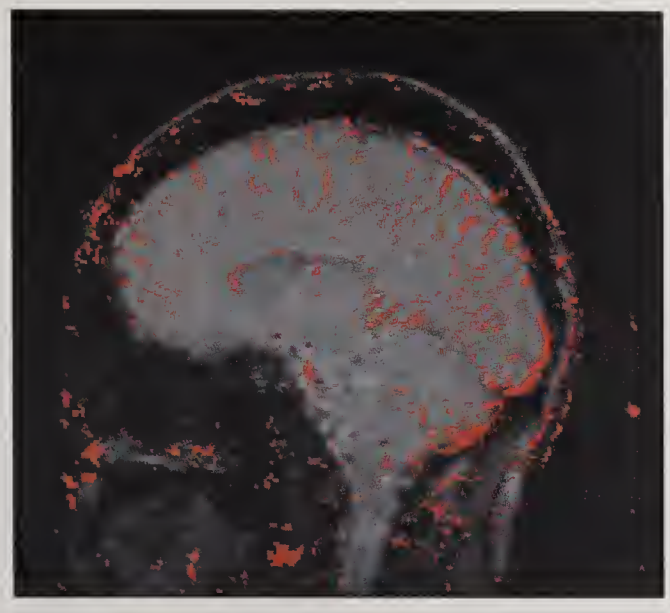

Figure 1a

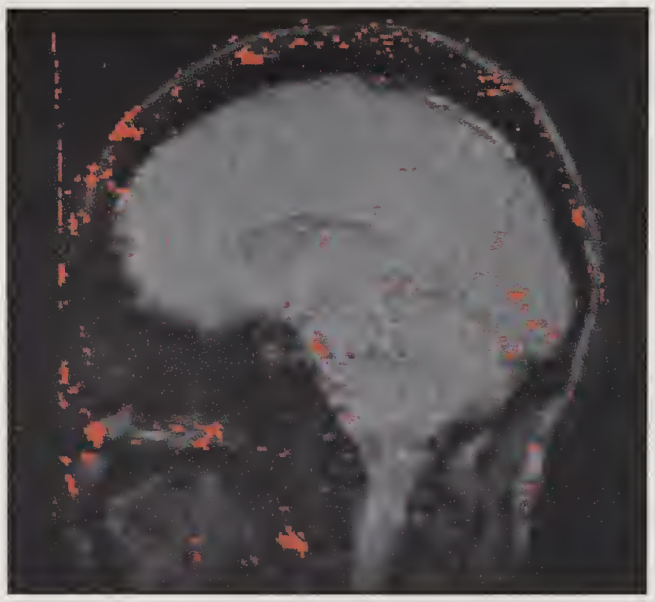

Figure 1b

Figure1: *The positive one-sided t-test (stimulus on > stimulus off) activation map prior to image alignment (1a) and after image alignment (1b). The noise remaining in figure 1b is likely a result of movement into and out of the plance, blood flow in the dural sinuses, and imperfections in the alignment algorithm.*

Introduction

Functional magnetic resonance imaging (fMRI) uses a series of magnetic resonance images to determine which areas of the brain are activated by the presence of a given stimulus. By using the technology of magnetic resonance imaging (MRI)[1-3], fMRI has an unparalleled ability to combine spatial and temporal resolution, while exposing the subject to no radiation.

In magnetic resonance imaging, the patient is placed in a strong magnetic field which tends to align the magnetic dipoles of hydrogen nuclei, especially in water, parallel or anti-parallel to the field [1-4]. In order to gather information about the dipoles, a short burst of radio-frequency (rf) energy is used to perturb them. In response to this perturbation, the protons release their own rf waves, which can be detected and presented as a digital image[1-4].

The digital image is made up of many rows and columns of picture elements (pixels), each representing a discrete volume in space. Each pixel is assigned an intensity value depending on the strength of the rf waves emitted from that region. Images are typically displayed using a gray scale, in which the pixel values are assigned shades of gray with the larger pixel values being whiter[1-4].

Functional magnetic resonance imaging maps brain activity through analysis of preferably more than fifty images of the same anatomical slice in the presence and in the absence of a stimulus[5,6]. Conventional stimuli consist of vision, sound and pain[5-7]. The images are divided into two groups according to whether they were acquired during stimulation (group 1) or control conditions (group 2). Pixels can be compared between the different images. The pixels are identified by their row and column (eg. pixel (10,35) is the pixel in the 10th column and 35th row of the image). Each pixel represents the same anatomy if the subject is perfectly still during the acquisition of the images[8]. Intensity differences at a particular pixel between images are thought to be the result of background noise, anatomical misalignment or brain activation[7-9].

According to the model that explains fMRI, active regions of the brain receive an increased blood supply[9]. This additional blood overcompensates for the increased metabolic demand and increases the ratio of oxygenated to deoxygenated hemoglobin (Hb)[6,9]. Since paramagnetic substances cause their surrounding space to appear darker on magnetic resonance images (MRI) and because deoxygenated blood is paramagnetic, the active region, which has relatively less deoxygenated Hb, is more intense than the control images[9].

Since the intensity changes due to brain activation are small (around 1-2%), statistical tests are required to determine if the differences between group 1 and 2 are significant. One method that is commonly used is the Student's t-test[6-10]. The mean intensity of each pixel is calculated in every image in a group, creating a *mean image* from that group. Mean images are created from group one and two. The difference of each pixel's intensity between the two mean images is compared to the variance of that pixel's intensity across all of the images. Larger differences relative to the variance are more significant and have a correspondingly lower p-value. An activation map derived from the t-test assigns a different color or brighter intensity to lower p-values. This activation map is superimposed on an anatomical image of the brain for orientation[6-11].

Since activated regions are more intense on images acquired under the presence of a stimulus[6-11], pixels in group 1 should be more intense than pixels in group 2. A positive one-sided t-test activation map highlights pixels that are significantly greater in group one's mean image, thus showing any brain activation. Similarly, a negative one-sided t-test highlights pixels that are significantly greater in group two's mean image and thus should not show any activation. Any apparent activation on this map is from misalignment or from other extraneous sources of noise.

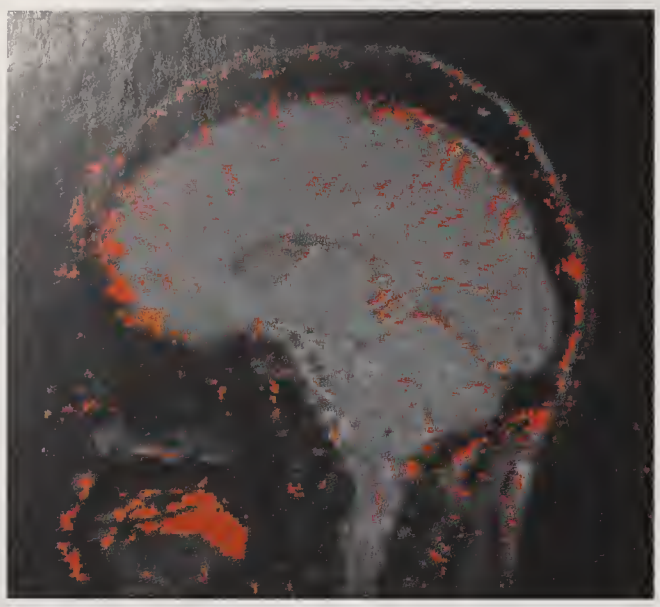

Figure 2a

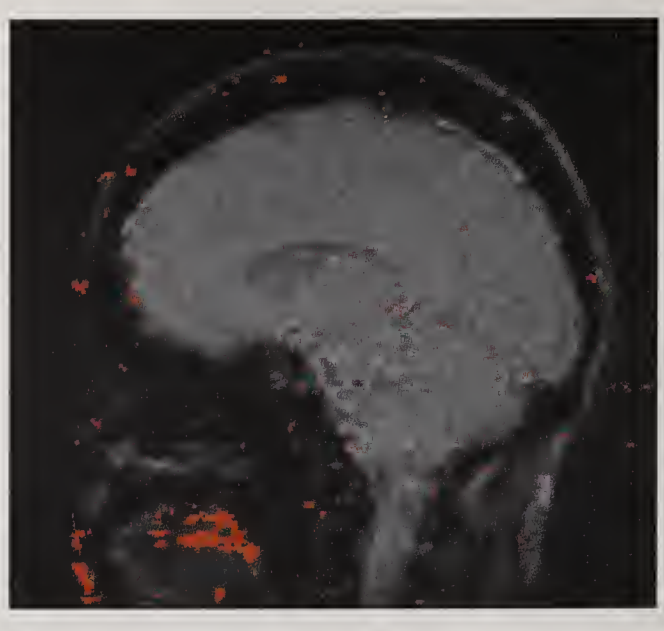

Figure 2b

Figure2: *The negative one-sided t-test (stimulus off > stimulus on) activation map prior to image alignment (2a) and after image alignment (2b).*

Our study addressed whether or not aligning images prior to statistical processing would decrease noise due to misalignment and thereby yield activation maps that could be more easily interpreted.

Method

Part A (Reduction of Noise by Alignment)

We collected our images from Dr. Karen Davis of the Playfair Neuroscience Unit, Toronto, Canada, using a GE Signa 1.5 Tesla MRI system (General Electric Medical System, Milwaukee, WI) at The Toronto Hospital, Western Division. A total of seventy-two sagittal magnetic resonance images were acquired, half taken with a stimulus present (group 1) and the other half in its absence (group 2). The stimulus used was a visual stroop test. In this test, the subject was told to look at text spelling the names of colors, for example "blue", "red", and "green". The letters of the word, however, were in a different color than what the word read. For example, the word "blue" might have been shown in green, red or yellow letters. The subject was instructed to concentrate on the color of the letters, not what the word read. With this fundamentally visual stimulus, the visual cortex was expected to appear active on the brain activation maps.

These images were processed using a computer automated algorithm developed by the authors to create the first set of positive and negative one-sided t-test brain activation maps. A red color scheme was chosen to emphasize all pixels that were different between group 1 and 2 with a p-value threshold of <0.001, and this threshold and color scheme were used on all of the subsequent brain activation maps in both Part A and B of the study.

In order to determine whether or not any movement had occurred during the acquisition of these images, they were displayed in a rapid sequential order, called a movie-loop. An objective indicator of misalignment was then calculated to confirm the observations from the movie loop. The indicator chosen was the root mean square difference (RMSD) between images. The RMSD quantifies the differences between two images by calculating the square root of the average of the differences of the pixel intensities between the two images squared:

$$\text{RMSD} = \left({}^{1}/_{n} \sum_{\text{all } j,k} \left(P_1(j,k) - P_r(j,k) \right)^2 \right)^{1/2}$$

where $P_1(j,k)$ and $P_r(j,k)$ represent the intensity of the pixel at column j and row k in image one and the reference image, respectively, and **n** is the number of pixels in each image.

The reference image was taken under control conditions (no stimulus present) midway through the acquisition of the seventy-two images. The RMSDs quantified how different each image was from the reference.

Using purposely misaligned images, the validity of the alignment algorithm developed by our laboratory was confirmed, and the algorithm was used to align the seventy-two images.

The alignment program required that a reference image be specified. All of the other images were then aligned with this reference; thus, the reference image was not rotated or shifted by the computer program. The same reference image was used in the alignment algorithm as in the RMSD calculations.

In order to verify that the images were aligned correctly, they were displayed in a movie loop and the RMSDs were recalculated. Because the alignment program had not altered the reference image, the RMSDs before and after alignment could be compared to determine if the images were more similar after alignment.

The computer automated processing algorithm was used on the aligned images to create the second set of positive and negative one-sided t-test brain activation maps. The two sets of activation maps were then compared.

Part B (Activation hidden by misalignment)

Magnetic resonance images for part B were obtained from the Playfair Neuroscience Unit in a similar fashion to part A. This time, seventy-two axial magnetic resonance images were acquired, half taken during painful stimulus of the right big toe (group 1) and the other half taken in the absence of stimulus (group 2). These images were processed with the same computer algorithm as in part A to create the first positive one-sided t-test activation map.

The images were then randomly misaligned using a computer algorithm which randomly selected degrees of rotation from a normal distribution with mean of zero degrees and a variance of two degrees, and a horizontal and vertical translation from a normal distribution of mean zero pixels and a variance of ten pixels. The misalignment of the images was confirmed by displaying them in a movie loop and calculating their RMSDs. The purposely misaligned images were processed using the computer algorithm creating the second positive one-sided t-test activation map.

The alignment algorithm was then applied to the misaligned images and a movie loop and the RMSD calculations were once again used to verify the realignment. This set of images was also processed creating the third positive one-sided t-test activation map. Finally, the three activation maps were compared.

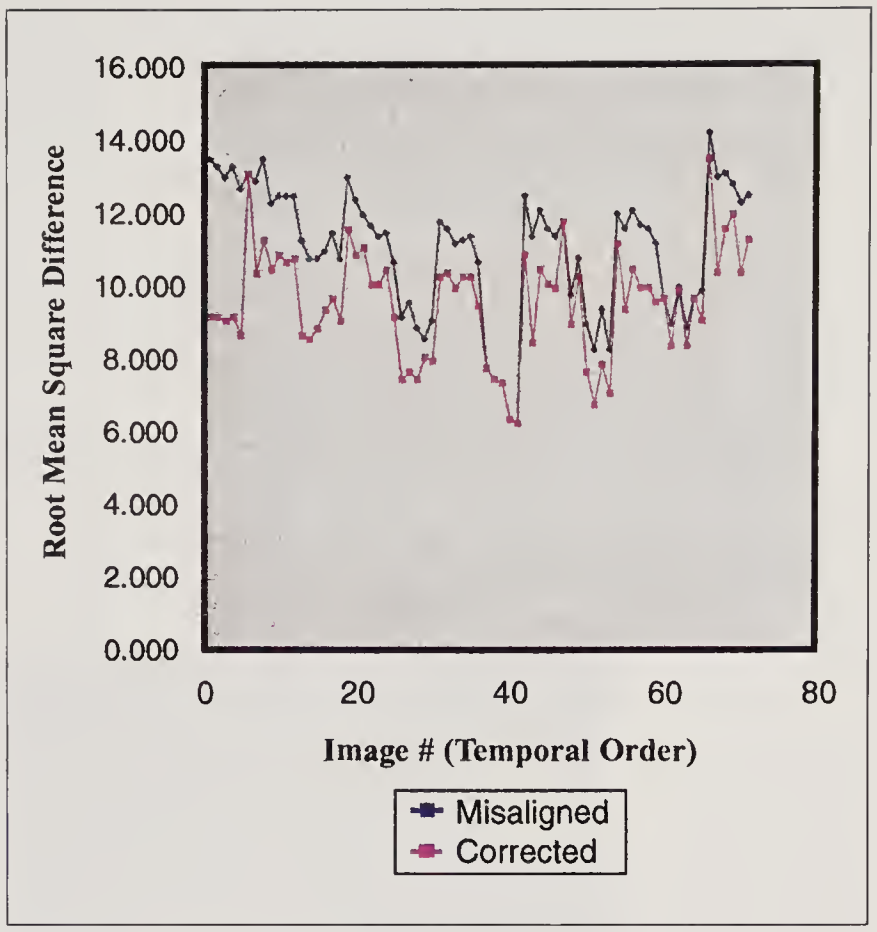

Figure 3: *The RMSD of the images with the reference image is plotted for the original misaligned images (blue) and the corrected aligned images (purple). The RMSD is decreased in the aligned images. The reference image was acquired after image #39 and before image #40.*

Results

Part A (Reduction of Noise by Alignment)

Both the positive one-sided (Figure 1a) and the negative one-sided (figure 2a) maps in the first set of brain activation maps were covered with highlighted areas (shown in red).

When the original images were displayed in a movie-loop in the order in which they were acquired, head motion was observed, specifically, nodding. The RMSDs were calculated and plotted in Figure 3, labeled as "misaligned".

When the images were aligned and displayed in a movie-loop, less motion was observed in the corrected images, but there was still some movement, particularly of the tongue. The RMSDs were calculated and plotted in Figure 3, labeled as "corrected".

The corrected images were then processed to create the second set of brain activation maps which had markedly reduced noise (Figures 1b and 2b).

Part B (Activation hidden by misalignment)

The first positive one-sided t-test brain activation map, created from processing the second set of images, showed a localized highlighted region in the sensory and pre-motor areas in the left hemisphere of the brain (Figure 4a).

The images used to create this map were then randomly misaligned. The resulting images were displayed in a movie loop and were observed moving randomly; their RMSDs were also elevated. The purposely misaligned images were then processed creating the second positive one-sided t-test brain activation map (Figure 4b) which showed no areas of activation.

The misaligned images were then corrected using the alignment algorithm and the resulting images were displayed in a movie-loop. Less motion was observed following correction of the misalignment, but there was more motion seen in the corrected images than had been observed in the original non-misaligned images. The RMSDs were likewise reduced but were still greater than in the original images.

The corrected images were processed creating the third positive one-sided t-test map (Figure 4c), which had almost the exactly same highlighted region as in figure 4a.

Discussion

Part A (Reduction of Noise by Alignment)

The RMSD quantifies the differences between images (see Figure 3). Since each image is not exactly the same because of blood flow, cerebrospinal fluid (CSF) motion, brain activation, movement, and noise, the RMSDs are not expected to be zero[13]. When there is misalignment, the RMSD will be greater, because each pixel is subtracted from a pixel in the reference image that represents different anatomy. Furthermore, the RMSDs will be greater when there are areas of stimulus-induced activation since the reference images were acquired without the stimulus present; however, because activation affects a smaller area of the brain and therefore a smaller number of pixels than misalignment, the increase will be less dramatic.

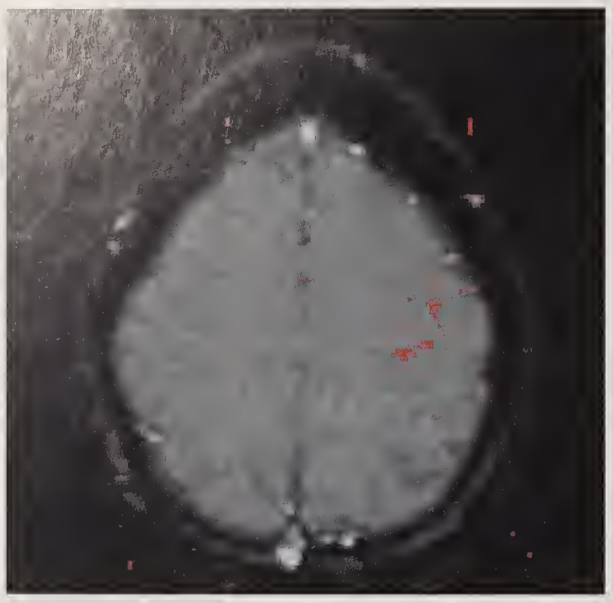

Figure 4a

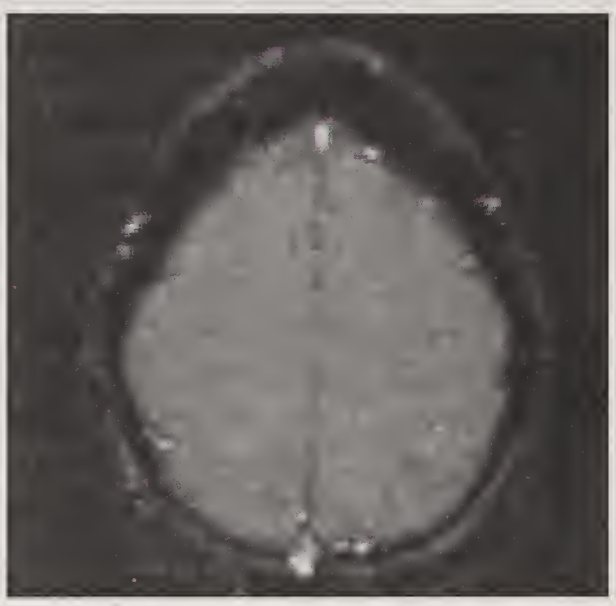

Figure 4b

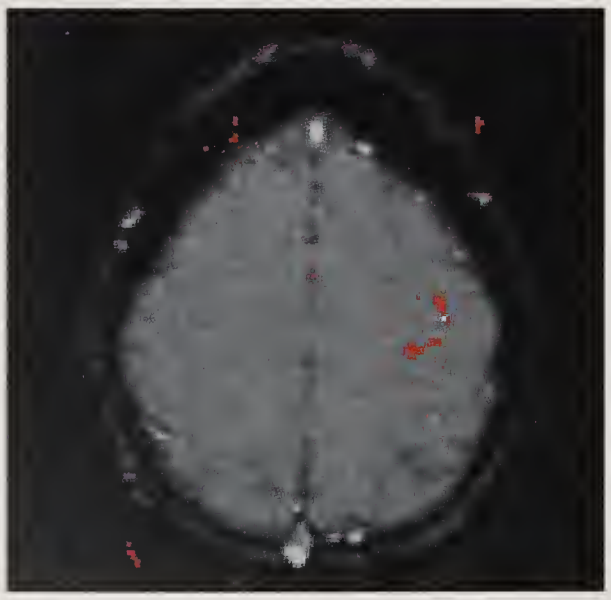

Figure 4c

Figure 4: *The positive one-sided t-test (stimulus on > stimulus off) brain activation map of the original images (4a), the randomly misaligned (4b), and the corrected images (4c).*

The RMSDs demonstrated a repetitive pattern of six relatively low values followed by six higher values. The smaller RMSDs belonged to the images taken without the stimulus present (group 2), while the larger RMSDs belonged to those taken with the visual stimulus present (group 1). Because the reference image was acquired under control conditions, one would expect it to be more similar to the images in group 2 than those in group 1. The increase in RMSDs in group 1 was likely due to two factors: stimulus induced brain activation and stimulus induced movement.

The comparison of the RMSDs of the original misaligned images and the corrected images confirmed that the alignment algorithm was successful (figure 3). The RMSDs of the corrected images were less than those of the original images, indicating that the alignment algorithm reduced pixel differences between the images and the reference.

The movie loops of the images before and after alignment confirmed that the alignment reduced the movement between images. The original images showed a head-nodding pattern when displayed in rapid sequential order. This movement may have been attributed to the subject having had to move his or her head to better see the visual stimulus. Once the images were corrected, the head no longer appeared to be nodding, although motion was still observed. This residual motion was likely due to limitations in the computer algorithm which is incapable of resolving motion outside of the images' plane, motion of internal structures such as the tongue and CSF, and blood flow[8,12-14].

The RMSDs and the movie loops demonstrated that there was stimulus-induced motion in group 1, and that the alignment algorithm reduced the misalignment caused by the motion.

The positive one-sided t-test activation map prior to image alignment (Figure 1a) was covered with red highlighted areas indicating pixels that were different with a probability of greater than 99% between the mean images of group 1 and 2. These areas could be due to brain activation, misalignment[8], blood flow[12] or noise[14]; however, the location of the region often suggests the cause. Obviously, any highlighted regions outside of the brain could not be due to brain activation. Furthermore, differences caused by misalignment would be most evident when neighboring pixels have significantly different intensities, and differences caused by rotation would be more noticeable further from the axis of rotation[13]. Finally, brain activation is localized[9] making it unlikely that the entire brain would be active in a diffuse pattern during a specific stimulus such as the stroop test. In Figure 1a, there were red regions outside the head which were dismissed as noise. There were also highlighted regions outside the brain, particularly on the scalp. These regions could not have been from activation, and were likely the result of rotational misalignment. Most of the red regions, however, were diffusely spread throughout the brain. These areas, referred to as areas of *apparent activation*, could be either regions of brain activation[9], or regions of *false activation* caused by misalignment[8], noise[14], CSF motion or blood flow[12,14].

Since the purpose of fMRI is to map brain activity, we wanted to eliminate the regions of false activation[6-11]. The positive one-side t-test activation map created from the corrected images had much less false activation (Figure 1b). In fact, the only noticeable region of apparent activation was localized to the occipital lobe, implying that much of the apparent activation in Figure 1a was due to misalignment. Given that a visual stimulus was used, it is not surprising to find that the remaining area of apparent activation is located in the occipital lobe[5].

Highlighted pixels in a negative one-sided activation map represent pixels that were more intense in group two's images (those taken under control conditions) than group one's images (those taken during the stimulus). Assuming that no areas of the brain were more active when the stimulus was absent, all highlighted regions within the activation map were areas of false activation. The negative one-sided t-test activation map, created from processing the original images showed considerable apparent activation (Figure 2a). The negative one-sided activation map created from the aligned images showed less apparent activation (Figure 2b), indicating that image alignment eliminated areas of false activation.

From part A of the experiment, we were able to conclude that misalignment between the mean images causes areas of false activation on the fmr image. Furthermore, by aligning the images prior to processing, we were able to produce an activation map with markedly less false activation.

Part B (Activation hidden by misalignment)

The positive one-sided activation map created from the original images collected for part B of the study showed a region of activation in the right-sided sub-motor and sensory regions of the brain (Figure 4a). Since the stimulus was a painful stimulation to the left big toe, the location of the activation was consistent with our expectations[14]. Evidently, there was less noise in this activation map than in the original activation maps from part A of the study.

After the images were randomly misaligned, the processing resulted in a positive one-sided t-test activation map without any apparent activation (Figure 4b). Once the misaligned images were corrected using the alignment algorithm, the activated region was evident again (Figure 4c).

In a t-test activation map, a pixel is highlighted when that pixel in group one's mean image is different from its corresponding pixel in group two's mean image, with a p-value of <0.001. In order for the p-value to be low, the pixel's difference must be large compared to the variance of that pixel calculated throughout the images. Random misalignment increases the pixel's variance, thus rendering the pixels' difference due to brain activation less statistically significant. In short, misalignment hides areas of brain activation in an fmr image.

Conclusion

The purpose of fMRI is to map brain activity. Our study showed that subject motion during acquisition of the images causes two problems. Firstly, average misalignment between the images acquired during presentation of the stimulus and those acquired during its absence cause regions within the brain to be erroneously highlighted in the activation map. These regions can be misinterpreted as areas of brain activity rendering the activation map more difficult to interpret. Secondly, when misalignment is present, areas of actual brain activation may fail to appear on the fmr image.

Lastly, our study showed that aligning images with a computer automated algorithm prior to processing results in activation maps which are more likely to detect truly active regions of the brain and have fewer areas of false activation.

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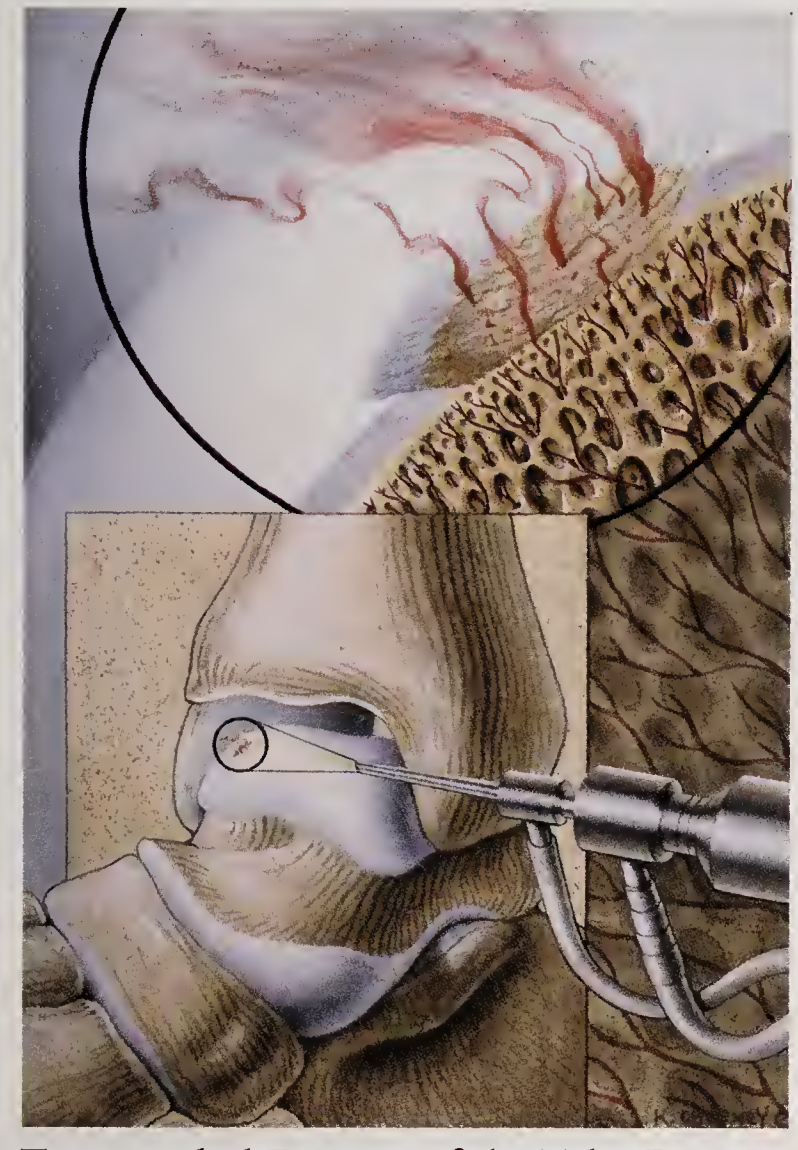

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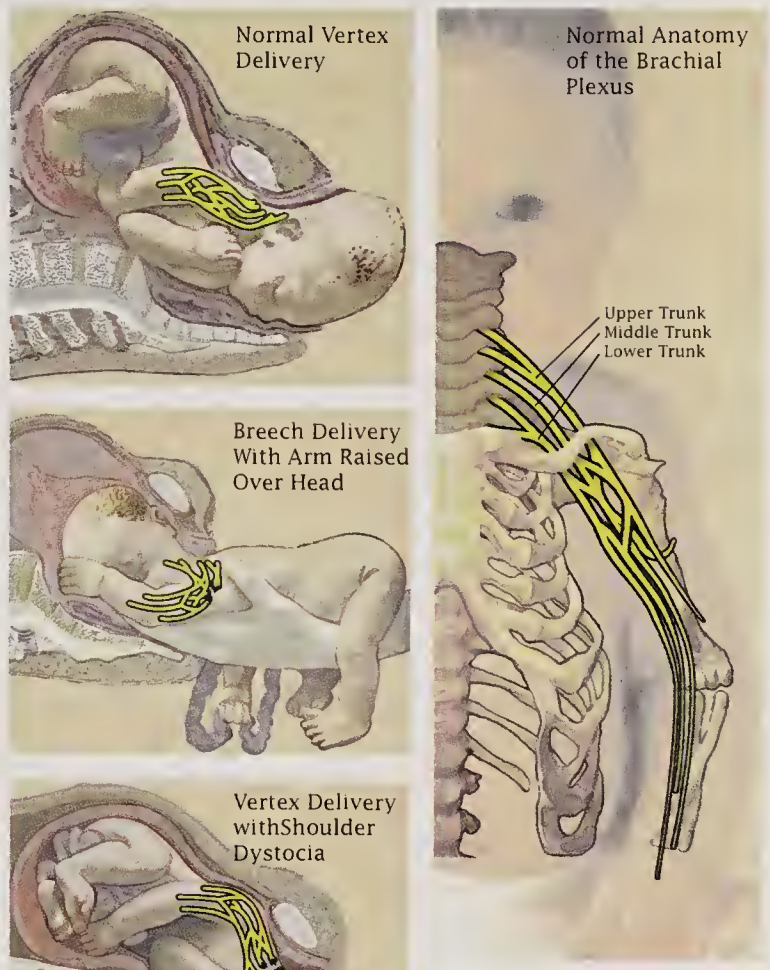

Obstetrical Brachial Plexus Lesions

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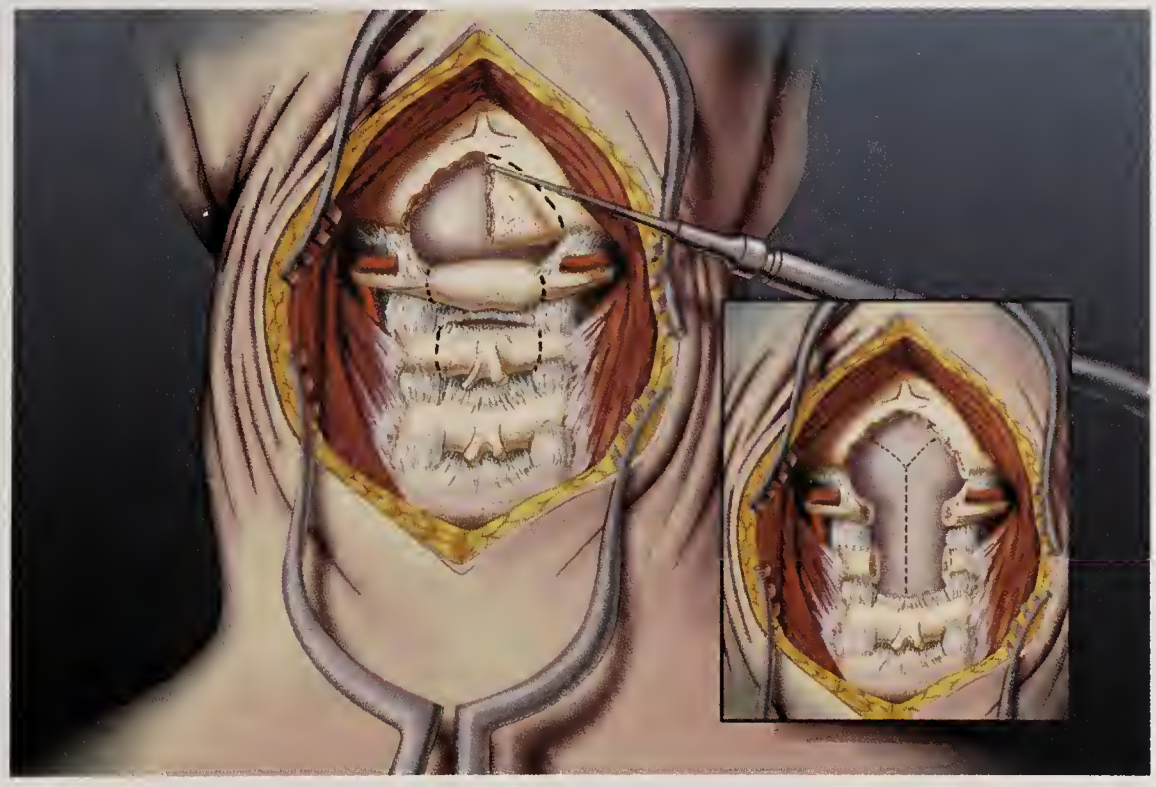

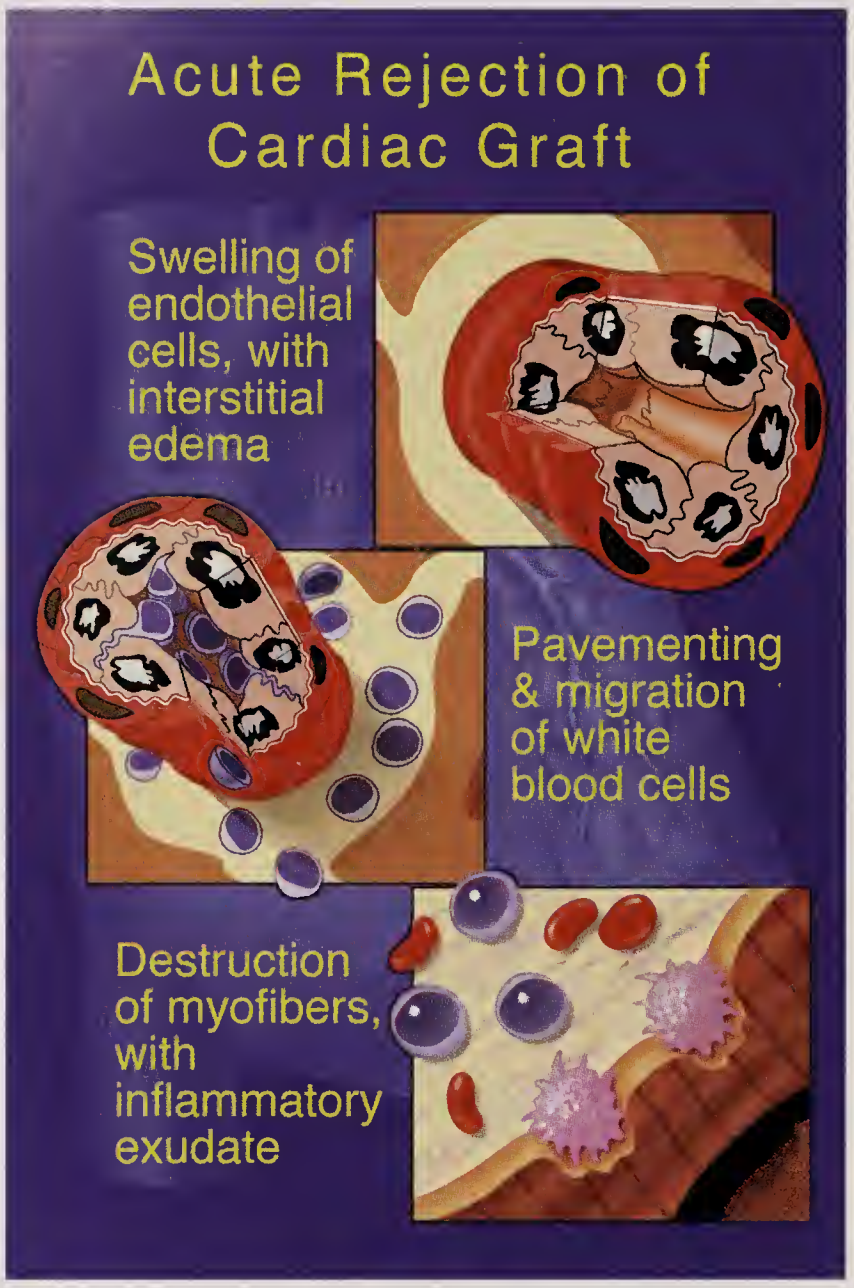
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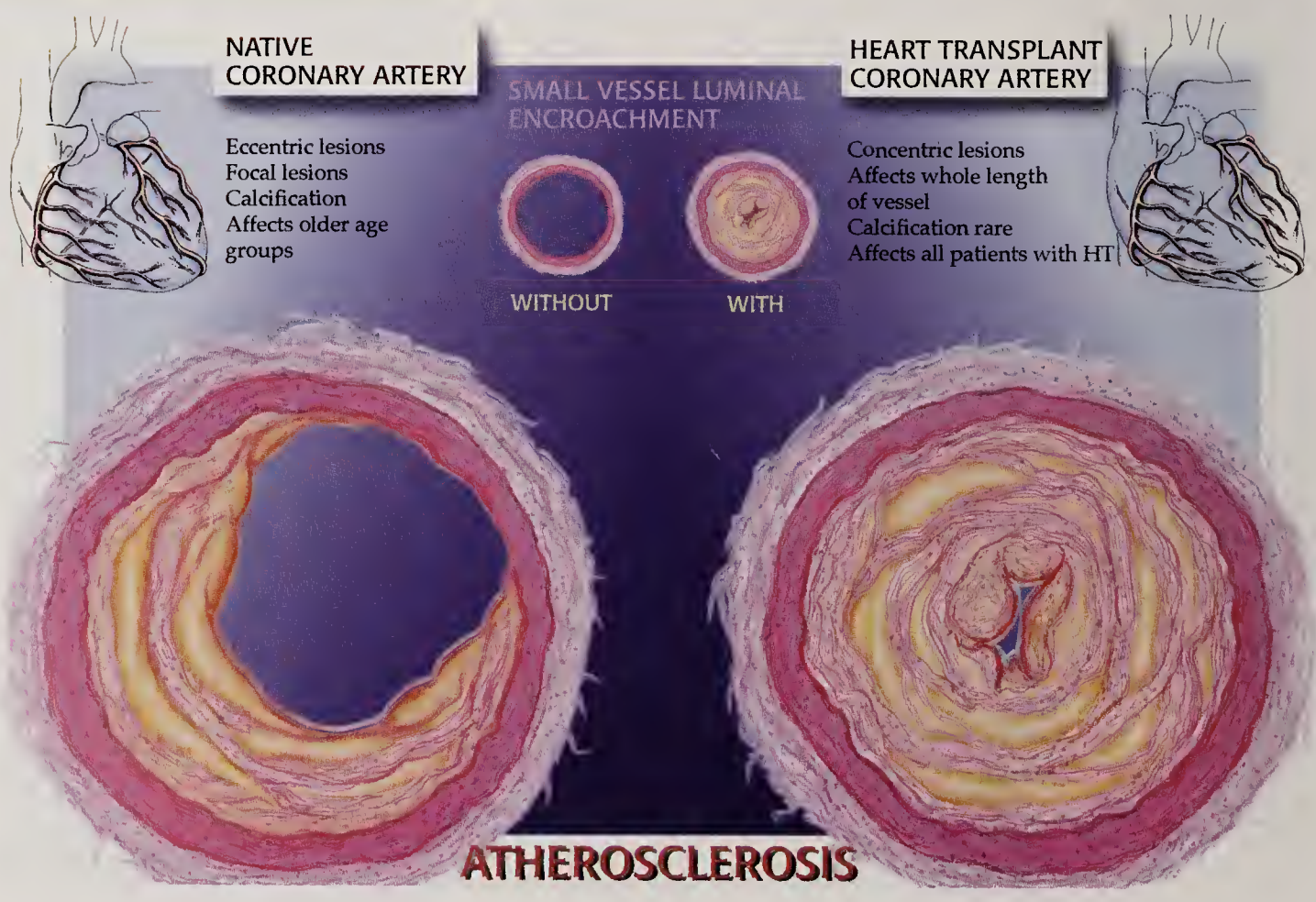

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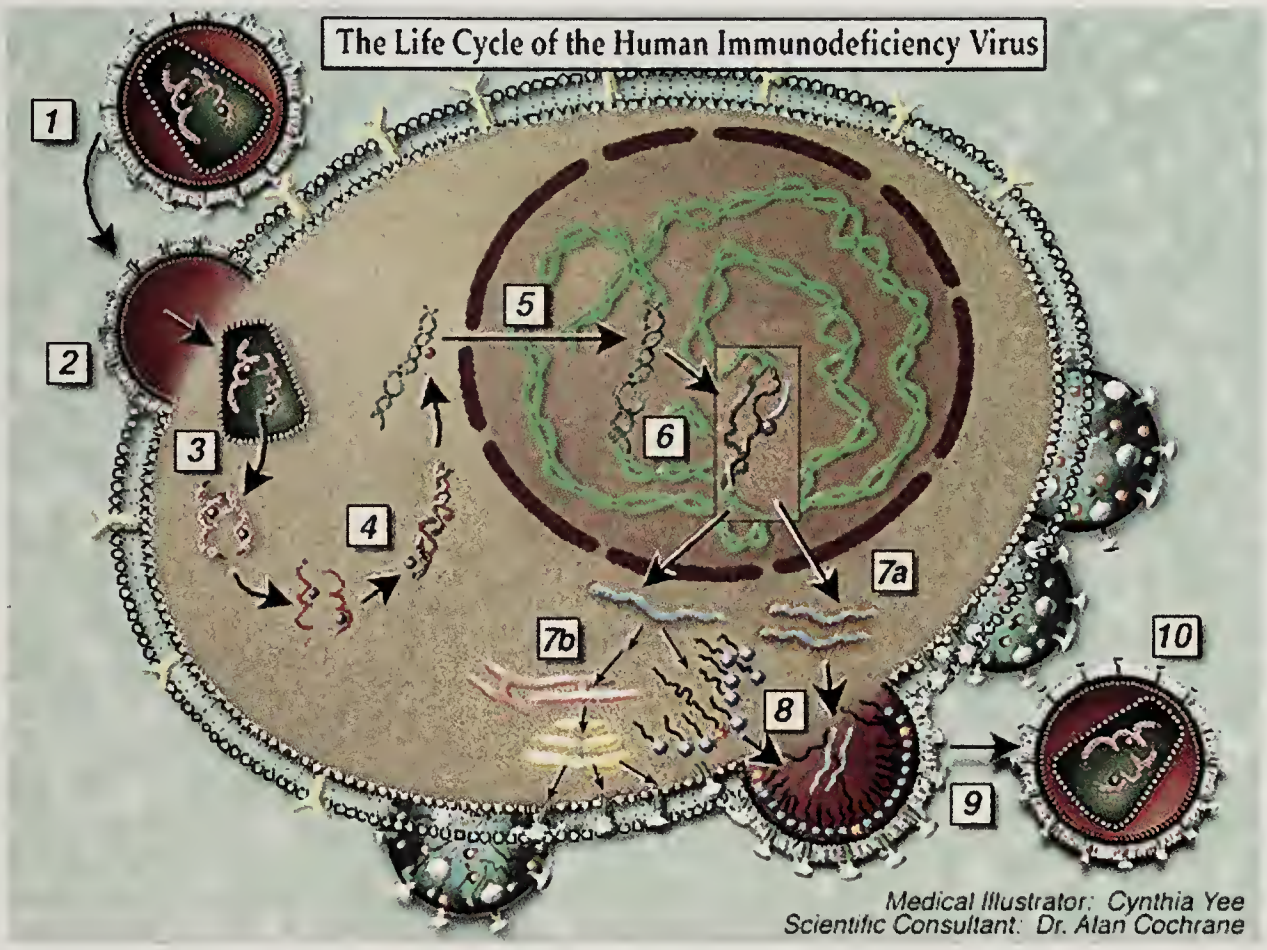

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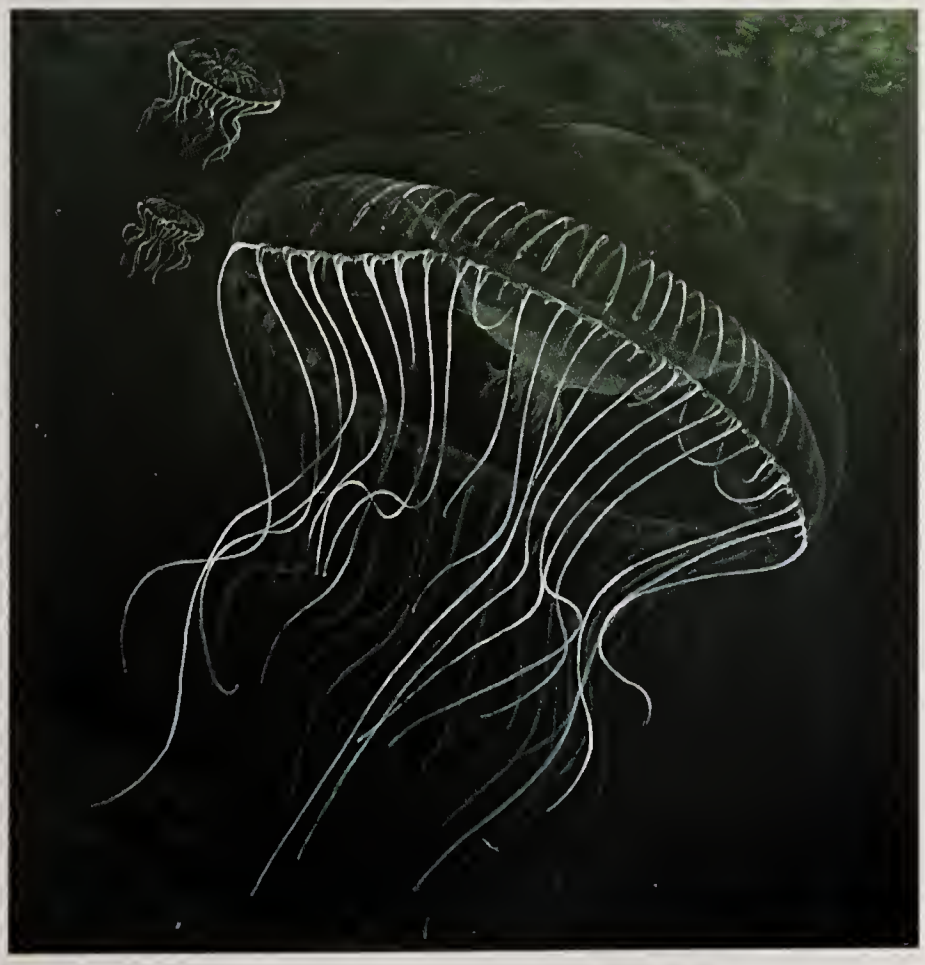


Aequorea Victoria
Jodie Jenkinson

Into the Amazon: Life with the Yanomamï Indians

Paul Kurdyak (9T7)

JOHN HARVEY

In the summer of 1995 I had the adventure of a lifetime. I went to the south-easternmost part of Venezuela, close to the Brazilian border, to live and study malaria drug-resistance amongst the Yanomamï Indians in a village called Coyowäteli. Prior to travelling to Venezuela, all I knew about the Yanomamï Indians was that they were, by virtue of the fact that they live in the middle of the inaccessible rainforest, a group of people who still lived by their traditional, semi-nomadic hunter-gatherer ways. They were, in fact, described by anthropologist Napoleon Chagnon as the most fierce and violent people on earth. I was both terrified and fascinated by the prospect of going somewhere so unbelievably remote and different. I am extremely grateful to have had the opportunity to have this experience, as those turned out to be ten of the most wonderful weeks that I have ever spent.

I went to study malaria. Malaria is a parasite that is transmitted from human to human by the bite of the female anopheles type mosquito. The parasite has an initial developmental phase in the liver. Subsequently, the parasites enter the blood stream where they invade red blood cells, multiply, and within 48 hours cause red blood cell lysis. The cycle of red blood cell invasion, multiplication, and rupture can be repeated many times. There are four different strains of malaria - Plasmodium malariae, P. ovale, P. vivax, and P. falciparum. The strains of malaria endemic to the region that I visited are Plasmodium vivax, and P. falciparum, the latter of which can be fatal, mostly because of the potential for developing cerebral complications such as generalized cerebral edema and inflammation.

Resistance to drug therapies is an increasingly common problem all over the world. Factors that lead to malaria drug resistance are mainly related to improper use of antimalarial medication - non-compliance being the main issue. Non-compliance is a serious problem even in developed countries where people have a fundamental understanding of the role of medication in the treatment of disease. With the Yanomamï, poor compliance is engendered by their culture, beliefs, and lifestyle. The Yanomamï have no exact system for keeping time - they maintain a general idea how much time has passed by tracking the cycles of the moon, but they have little need for marking days off a calendar. They have two numbers in their vocabulary - one

A ritual battle between adjacent villages

Isolated Yanomama looking at images from modern life

and a couple. Obviously, these factors make it very difficult to prescribe a medication that has to be taken for 14 days at the same time every day. They do not believe that malaria is spread by a mosquito - to their thinking, malaria is a curse or witchcraft put upon them by an enemy from a hostile village. Sometimes I would find the medication I sent with them carefully wrapped in a small palm leaf and worn as a charm around the neck to ward off malarial spirits. Finally, food is much more important to them than finishing a treatment that they do not really believe is working. When they run out of food, they simply sling a hammock on their back and trek through the jungle foraging.

My project involved diagnosing malaria among those people with a fever. The missionaries with whom I stayed had a microscope that I used to look at blood films. If I found evidence of parasitemia, I initiated treatment and then took a small sample of blood from them 4 times over 14 days. The samples are now being analyzed by the traditional microscopic method and by polymerase chain reaction (PCR), a technique for looking at malaria DNA levels in a tiny blood sample. The result is a plot of the response of the parasite to treatment over a 14 day period. In this way, we can quantify the extent to which the strains of malaria with which the Yanomamï are being infected are resistant to the drugs with which they are being treated.

Of course, not all of my time was spent working on the project. I had the opportunity to spend time with the villagers, getting to know what it is like to be a Yanomama. At first, I went through a period of culture shock. Many things about my environment contributed to this - I was very isolated. The only contact that I had with modern civilization was by radio to the nearest frontier town. A plane carrying supplies came in sporadically on a loose two-week schedule. Beyond the airstrip, there were many paths that led into the jungle, but it was impossible for me to even consider venturing out unaccompanied. Twenty feet in, the jungle swallows you whole and the paths intertwine chaotically and change weekly on account of the tremendous growth rate of the foliage. I slept in a hammock for the entire ten weeks - a practice that took some getting used to. The jungle erupted with noises at night, some of them strange and foreboding. One of the louder noises sounded like a dog barking; I later learned that the source of this noise was a small rodent.

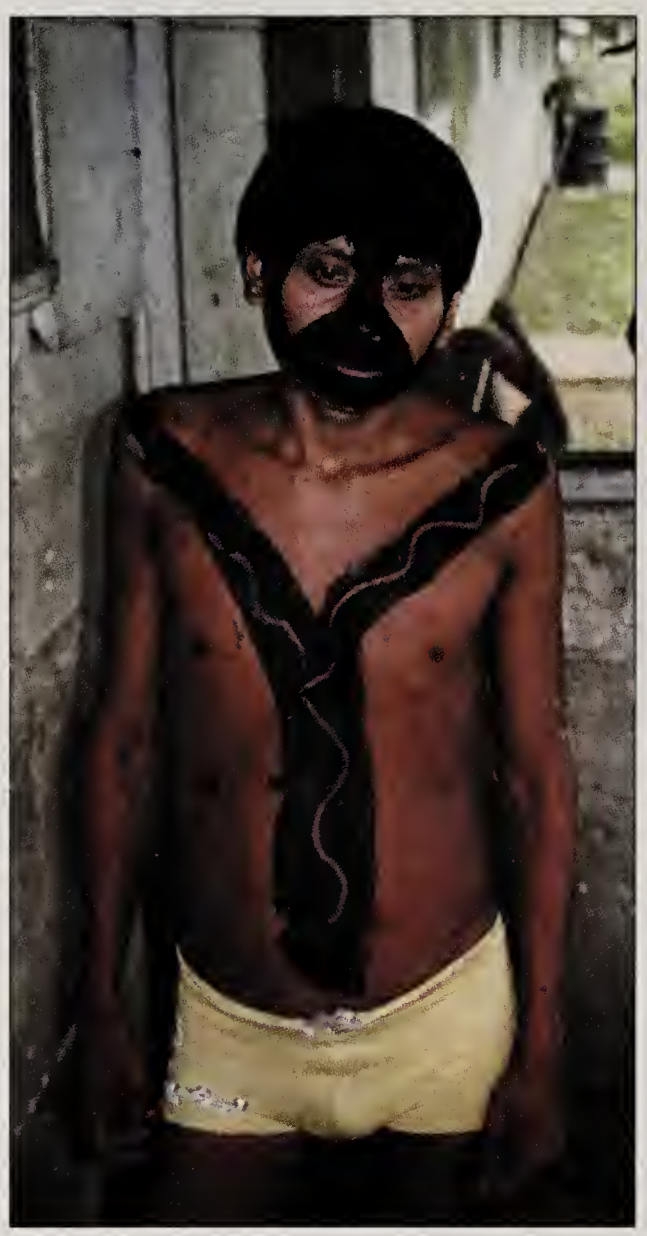
Initially, the Yanomamï were very curious about my purpose there. Most other visitors have come for only a week or two. After my first two weeks, the villagers were surprised that I was still around. They had a different sense of privacy and personal space. They would often stare at me through the screen door or breathe down my neck as I looked at microscope slides, trying my best not to notice. Even I myself was a curiosity - I quickly gained a status akin to being the village clown and pet. They would not hesitate to come up to me and feel the hair on my arms (they have virtually no body hair) or to take my glasses from me and try them on. They would also love to have me along on their day-long treks to their gardens or into the jungle. Everything I did was a source of amusement- the way I walked, the way I got so sweaty and dirty. They only cleared the trails to their height, which was, on average, usually a full foot shorter than my six feet. Banging my head on low hanging vines apparently made for some classic Yanomamï slapstick.

Occasionally, our two cultures would clash in embarrassing and amusing ways. When they are within the household of a good friend, they can ask for anything that the host has and the host is obliged to give that item. They took advantage of this custom when I first arrived and asked for the food and the t-shirts that I brought. When I flatly refused their requests, they would say, in a huff, "fine, see if I ever ask you for anything again", as if that were a hurtful insult.

During my stay, I lived in the home of a family, the Jank's, that is affiliated with the New Tribes Mission. In Marg Jank's house, the environment where I was comfortable and the Yanomamï felt awkward, I was constantly amazed at how they behaved. They preferred to squat on the cement floor rather than sit on chairs or benches because they complained that chairs made their back sore.

The tribesman who called me "shorlicaba" (big, old brother-in-law)

I brought pictures of close friends and family with me to Venezuala. One day, the inhabitants of a nearby village with virtually no contact with Westerners passed through. When I showed these visitors my pictures, they were unable to make out the images. They literally could not see the images of people; I think that they only saw a blur of colour. It was only then that I realized that our ability to make sense and to interpret two dimensional images is a learned skill. Similarly, when I went with them into the jungle, they would often point at something in the distance like a monkey or a bird and all I would see is foliage. They later told Marg that while I was walking in the jungle, I looked around a lot, but I couldn't see a thing. They also couldn't understand why I couldn't keep up with the oldest women of the village on our treks through the jungle, yet in our almost daily soccer games on the flat and manageable airstrip, I could outrun, with my long legs, the fastest man of the village.



Traditional warrior face paint of the Yanomamï

After a time, my interaction with the Yanomamï started to change in a subtle, yet perceptible way. They asked me to go on expeditions with them not because they wanted to laugh at my strange ways (although they really couldn't resist laughing at my expense), but because they enjoyed seeing my wonderment at the way they lived. They also grabbed my arm and took me to their dwellings and threw plantains on the ever-present fires. This universal gesture of friendship was especially meaningful to the Yanomamï because food is of central importance and, indeed, their main pre-occupation. When they started to sense that I was soon to leave, the Indians with whom I was closest started to ask me for things that they had no use for, but were symbolic of me. For instance, one good friend of mine who called me shorlicaba, which means big, old brother-in-law, asked me for my glasses. Another asked me for my funny-looking sandals and my belt despite the fact that their feet are tougher than any leather and they usually wear loin cloths.

Ten years ago, anthropologists estimated the Yanomamï population at 30,000. Today, it has been reduced by one-third. Deforestation, brutal killings by illegal gold miners in the north of Brazil, and malaria are taking a heavy toll on the Yanomama. It is a very telling and sad commentary to see that, despite their complete isolation in the heart of the rainforest, they are still harmed by the environmental havoc done in the name of development. The realization that they are a dying people added a sense of shame to the sadness I felt when the plane came to pick me up. The people with whom I lived are largely ignorant of the seemingly inevitable changes to their world and to their people. Indeed they live day-by-day and assume that the world is one big rainforest. In their minds, the plane had to take me back to Canadateli, or village of Canada, because it was too far for me to walk.

At some elemental level, however, I think that the Yanomamï do understand what is going on. One remarkable incidence suggests that. I was walking in the jungle with Bobby Jank and two of the hunters from the village, hunting menashi, or wild turkey. The Yanomamï carry machetes with which they blaze a trail. Occasionally, they will take a swipe at a big tree at the side of the trail to mark it just in case they get lost. On this occasion, one of the hunters was hacking violently at almost every tree he passed (in a rainforest, this kind of activity can slow you down considerably). Bobby asked him why he was doing this, to which the hunter responded that he was angry. Bobby then inquired as to why he was angry. This kind of question always takes them aback; they are unaccustomed to people asking why they feel the way that they do. However, we stopped and he thought for a couple of minutes and responded, "I am angry because these trees are still here and my people are not."

Acknowledgements

I would like to acknowledge the wonderful hospitality and support of New Tribes Mission and the Jank family with whom I stayed during my visit. Also, I would like to thank Dr. Kevin Kain for helping me to develop this project, enabling me to have this incredible summer. Finally, and most importantly, I would like to acknowledge the warmth and kindness the Yanomamï extended toward me while I was in their village.

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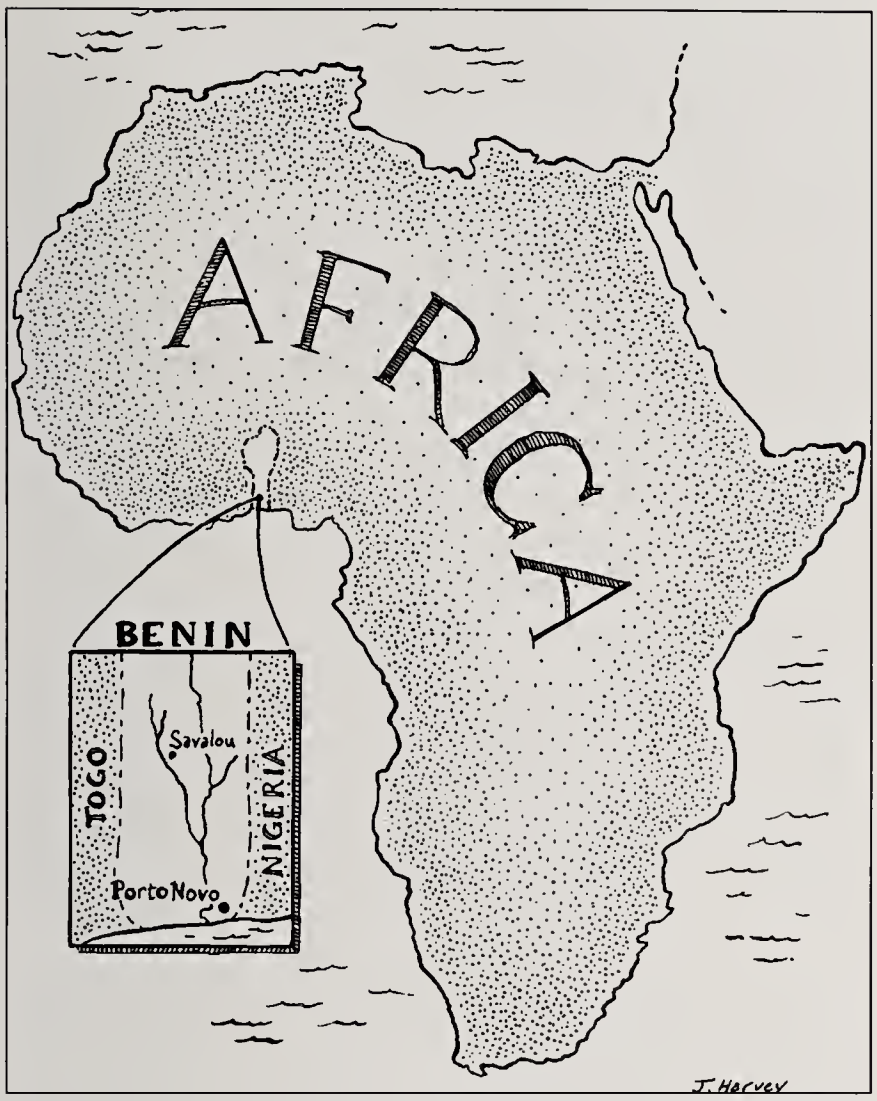
A *Yovo* in Bénin, West Africa

Colin Lee, B.Sc. (9T8)



JOHN HARVEY

Medical students at the University of Toronto are fortunate to have the opportunity to participate in exciting, ground-breaking research at the university teaching hospitals. Why then, would one travel thousands of kilometres to conduct research in a developing country such as Bénin? I faced this question from many of my first-year classmates when I decided to delay returning for the second year of the medical program, and instead elected to remain in Savalou, Bénin for the academic year of 1994-95. In 1994, the Faculty of Medicine's International Health Program (IHP) offered me the chance to continue a three month research project on malaria that I had previously developed in West Africa with the United Nations Volunteers/ United Nations Development Program (UNV/UNDP).

Malaria is a protozoan disease that is transmitted by the bite of the female *Anopheles* mosquito. The malaria parasite is endemic in over a hundred countries and causes approximately one million child deaths in Africa alone each year. This infection is particularly dangerous for children under age five. In fact, during my seven month placement with the UNV, several infants and children whom I knew succumbed to malaria. The purpose of my study was to examine attitudes toward malaria and methods of malaria prevention in children in the rural setting. The study was a component of an International Development Research Centre (IDRC) project on the local fabrication and use of permethrin-impregnated mosquito nets in the region of Savalou. The results of my project were intended to suggest adaptations and improvements both to current malaria prevention methods and to educational programs on malaria prevention in children.

As a *yovo* (this is the local term for a white man; I could not convince the local population that I was Chinese), I soon realized that personally conducting interviews and focus groups with the villagers would be almost impossible. Although French is the official national language of Bénin, the majority of the population uses any one of over 100 different languages and dialects. Fortunately, a women's cooperative called *Nyona,* which had become well-known in the villages through its involvement in the mosquito net project and in maternal-child health programs, was able to provide facilitators and translators.

Entering a village to conduct focus group discussions was a complicated affair requiring a formal meeting with the village elders two weeks in advance in order to explain our purpose and to gain acceptance from the villagers. The *méwi* (locals) believed the *yovo* to be more advanced, especially with respect to medical issues and they did not understand our purpose in gathering information from them about malaria. Some suspected that our research had an exploitative ulterior motive, while others assumed that we were bringing in free malaria medication. These disconcerting attitudes have their origins in the era of colonial rule in Bénin when the local population was marginalized by foreign powers. Although the slave trade in this country has been dismantled for over a hundred years, the influence of colonialism remains prominent in the mindset of many Béninese.

Tchinkoumé Dancing & Drum

Focus group discussion

Going to the village

Likely due to the acceptance that *Nyona* and the IDRC enjoyed on account of their long-standing grassroots involvement with the population, we were usually given the blessings of the elders and *Mawu* (God) to proceed with our focus groups and interviews. The sessions had to take place before sunrise as it was the rainy season and the villagers were eager to tend their crops of corn, manioc, yam, beans and gombo which they rely on for sustenance and income. Following our pre-dawn interviews, the villagers would embark on the five kilometre walk to the fields, carrying their tools, food, and water on their heads.

I had to wake up at 5:00 am to arrive in the villages on time. Eventually, I managed to train the chickens I was raising to give me a continuous "cock-a-doodle-do" wake-up call until I slipped out of bed to feed them their breakfast. The early mornings were a temporary sanctuary from the humid 40 degree Celsius heat of the day and provided an opportunity for my morning jog with my dog alongside me. This doubled as a source of entertainment for the Béninese who looked on in amazement and remarked, "The *yovo* is crazy! He is running and being chased by his dog for no reason. The voodoo must have gotten to him!". Bénin is arguably the epicenter of the *Vodoun* (Voodoo) religion, and many illnesses, deaths and other phenomena are attributed to sorcery.

On one occasion, the village that we were visiting was 35 kilometres away and the previous night's rain had turned the dirt roads into slick and muddy trails. We debated the notion of trying to fix another date but as many of the villagers would be occupied with the planting for the next month, another date may not have been possible - especially since the heavy rains had complicated the work. We decided that it was "now or never" if we wanted to talk to the villagers. We arrived in the village on our motorcycles and mopeds almost two hours later, drenched in mud courtesy of both the horrible road conditions and the pigs that would dart in front of our paths, seemingly from nowhere.

After drying off, we assembled the villagers under the Neem tree. The discussions were conducted in separate groups of women and men, as the women were reluctant to express their views in mixed groups. Women occupy a low status in that society and are not accustomed to actively participating in discussions. Nevertheless, the Béninese woman is strong both mentally and physically - working much harder than the man at fetching water and wood, cooking, caring for the children, and tending to the fields. Her keen business sense is evident when she walks to the nearest market every few days to sell the family's produce.

Our discussions with the villagers revealed that in order to prevent malaria, they had pooled their money and purchased 50 mosquito nets; a quantity sufficient for everyone to sleep soundly and safe from the infecting insects. An organized village such as this one is the exception, but the spirit of cooperation that we observed there encouraged us to continue our efforts in other villages.

After the discussions, everyone was in a festive mood. The hunters of the villages offered us an antelope, and the women provided cornmeal, yam and vegetables. While the meal was cooking on the fire, the *tchinkoume* traditional music group started drumming on their large calabashes and *tam-tam* drums and dancers, some as

Going to the market

young as five years old, moved in unison to the rhythm of the music.

Ultimately, we were guided toward the dwelling of the *Da* (chief) with whom I had been granted an audience. After completing the greeting formalities, he signaled for the "medicine" called *sodaby.* This liquor, with a 50% alcohol content, is distilled from the wine of a palm tree, and is customarily offered to visitors arriving at one's house. In order to demonstrate that the drink was free of any poison, the *Da* poured and drank a few drops before offering me an overflowing glass. The Béninese were always entertained by the redness that flushed my face and body after alcohol ingestion, and it was always a chore for me to explain that I lacked the enzyme necessary for alcohol metabolism. Before gulping the rest of the *sodaby,* I held the glass in my hand and spilled some on the ground as an offering to the *Da's* ancestors. Béninese generosity was reflected in the lavish meal of pounded yam, *gombo* (okra) sauce, spicy peanut sauce with *agouti* (giant bush rat) and antelope.

As I left the village, I pondered the daily challenges and obstacles that each of them face. The concerns of the villagers were reflected in the voices of the 200 participants of the group discussions and interviews. Later, as I listened to the transcripts, it was difficult to associate the participants' voices with the happy and festive smiles they wore on their faces during the celebration that they held for us. One villager lamented:

> "Malaria kills nothing but children. Here in the village, it is malaria that kills us the most. We do not understand it. We spend all our money trying to cure the fever and convulsions, but if God is not with you, the child will die. We try our best to prevent malaria in our children but it is to no avail."

One of the main reasons cited for their inability to practice effective malaria prevention was the lack of available finances to pay for chloroquine tablets and mosquito nets. They also feel powerless to prevent malaria in their children because they perceive the disease to be transmitted by a multiplicity of unavoidable agents including the sun, mosquitoes, heat from the fire, overconsumption of peanuts, and sorcery. One young mother of three exclaimed:

"Sure we can buy mosquito nets to prevent malaria from the mosquito, but what about the sun? We have to work in the fields in the hot sun. We might not get malaria from the mosquito, but we will get it from the sun."

Remarkably, the villagers consider the sun to be the principal agent of malaria and the mosquito is not widely believed by them to be associated with the disease. The villagers believe that the most frequent and serious malaria attacks come during the dry, hot season, when the sun is strongest and there is scant rainfall. In truth, there is little stagnant water available during that time and the dry season is most inhospitable for the breeding of malaria-transmitting mosquitoes. The deep-rooted connection between the sun and malaria is obvious from the local name given to the disease, *ouevozon,* which directly translates as "the disease of the sun". This fascinating finding prompted the research team to conduct additional anthropological and medical studies.

During Bénin's rainy season, villagers are often infected by the *Anopheles* type mosquitoes but do not achieve the level of parasitemia that is associated with the clinical disease state. The sun's ultraviolet-B (UVB) rays are recognized as a strong immunosuppressor,[1] and during the cotton-picking season in Bénin, the UVA and B readings can reach extremely high levels. One can speculate that the associated immunosuppression might disturb the equilibrium that exists between the malaria parasites and the immune systems of asymptomatic carriers thereby rendering the host susceptible to disease progression. This theory could account for the villagers' impression that malaria attacks are more frequent during the hot, dry season than during the rainy, wet season. It is of interest to note that the most popular method of malaria prevention practiced in the Savalou region consists of taking a daily morning drink that is made by boiling various green leaves. These leaves may contain different amounts of beta-carotene and other immune stimulants and one could further speculate that these agents confer some protective effect against the immunosuppression caused by exposure to the sun.

The collaboration between the research team and the villagers for the sun project was very successful. The Savalouans were excited that we listened to them and began to explore their centuries-old beliefs. I found this project interesting from a medical and scientific point of view; however, the strong bridge of ideas, goals and culture between the researchers and the villagers was what made this experience so exceptional. Now, hardly a day goes by without my thinking about the village researchers I worked with, the children who taught me the local language, and the dancing, fun, conversations, and emotions that we shared. Although we were from vastly different worlds, we discovered one essential common factor, and that was humanity.

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Paediatrics Rounds

Danyal Ibrahim, M.Sc. (9T7)

The Journal will be offering a prize of **$50** to the reader who submits the correct diagnoses for all the cases. Responses should be sent to the following address no later than **August 30, 1996.**

Quick Diagnosis Competition
c/o Danyal Ibrahim - Quick Diagnosis Editor
University of Toronto Medical Journal, Room 2141, Medical Sciences Building, Toronto, Ontario M5S 1A8
Email: danyal.ibrahim@utoronto.ca

Case 1

Jessica Macnab MD, CCFP, FRCP (C)

Clinical History

This three year old infant is being evaluated for fever and a cough. Here is his CXR.

Figure 1: AP Chest CXR.

Figure 2: Lateral CXR.

Does he have pneumonia?
What is this CXR finding called?

Dr Macnab is a staff Emergency Physician , Sunnybrook Health Science Centre and The Toronto Hospital.

Case 2

Jessica Macnab MD, CCFP, FRCP (C)

Clinical History

This child accidentally ate some pills.

Figure 1:
Abdominal X-ray.

List three toxic substances which are radiopaque on x-ray.

Dr Macnab is a staff Emergency Physician , Sunnybrook Health Science Centre and The Toronto Hospital.

Case 3

Jessica Macnab MD, CCFP, FRCP (C)

Clinical History

This nine month old child presents with a fifteen hour history of crampy abdominal pain and bilious vomiting.

Figure 1: Supine abdominal X-ray.

Figure 2: Erect abdominal X-ray.

Figure 3: Air Enema

What type of bowel obstruction does this child have?
What do you think may have caused this obstruction?

Dr Macnab is a staff Emergency Physician , Sunnybrook Health Science Centre and The Toronto Hospital.

Case 4

Jessica Macnab MD, CCFP, FRCP (C)

Clinical History

This two year old was brought by his parents because they fear he may have ingested a coin.

Figure 1: AP CXR

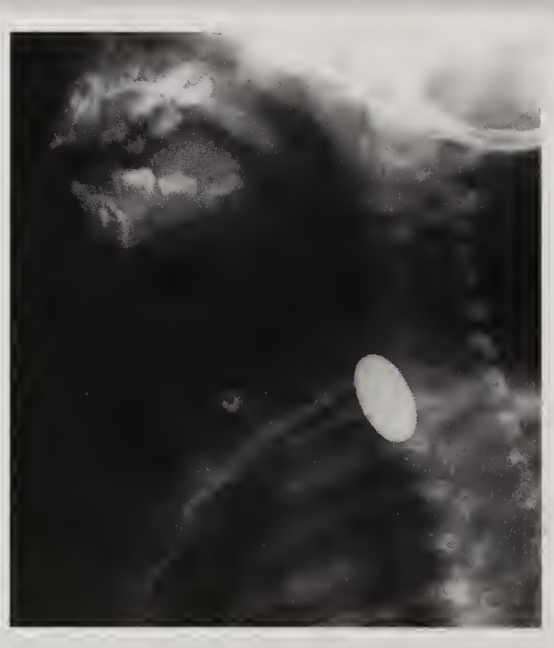


Figure 2: Lateral CXR

Where is the coin?

Dr Macnab is a staff Emergency Physician , Sunnybrook Health Science Centre and The Toronto Hospital.

Case 5

Jessica Macnab MD, CCFP, FRCP (C)

Clinical History

This fourteen month old Ethiopian child who was otherwise healthy but described as fussy eater, is brought in by his parents because they are concerned that he "walks funny" and seems to have crooked legs.

Figure 1: Plain X-ray of both knees.

Figure 2: Plain X-ray of hand.

Given these X-rays what is the diagnosis?

List three causes of this condition.

Figure 3: CXR

Dr Macnab is a staff Emergency Physician , Sunnybrook Health Science Centre and The Toronto Hospital.

Case 6

Jessica Macnab MD, CCFP, FRCP (C)

Clinical History

This thirteen year old obese male presents with a limp and hip pain.

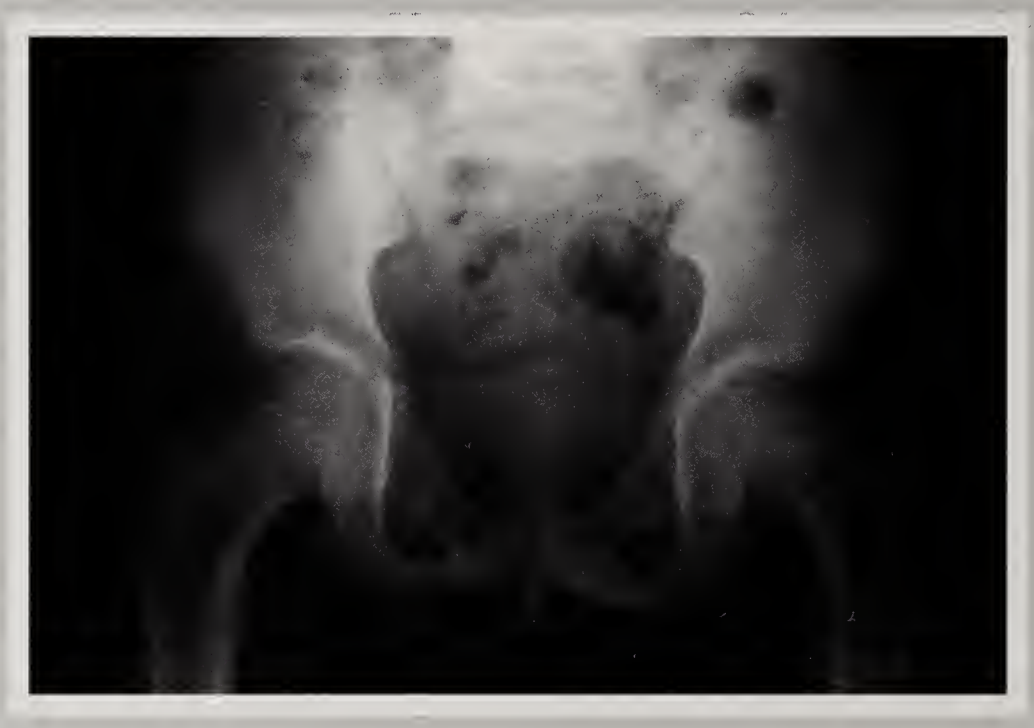


Figure 1: Plain X-ray of both hips

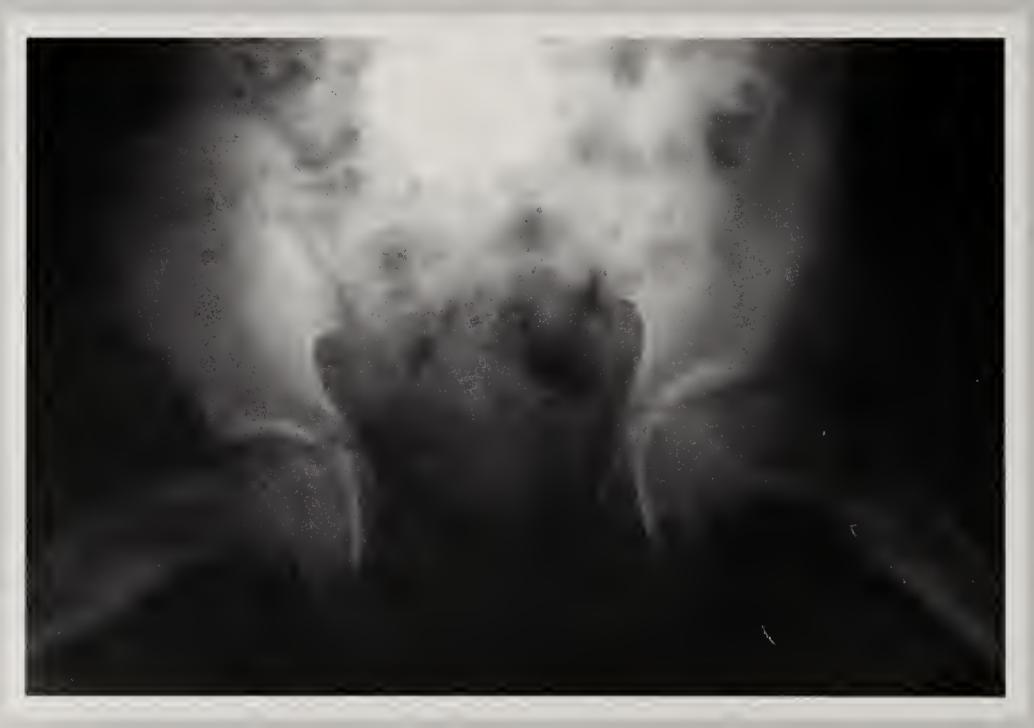


Figure 2: Plain X-ray of both hips (frogged view).

What is the diagnosis?

Dr Macnab is a staff Emergency Physician , Sunnybrook Health Science Centre and The Toronto Hospital.

Case 7

Jessica Macnab MD, CCFP, FRCP (C)

Clinical History

This small child presents with a two week history fever and a painful swollen elbow.

Figure 1: Plain X-ray of elbow.

What is the diagnosis?

Dr Macnab is a staff Emergency Physician , Sunnybrook Health Science Centre and The Toronto Hospital.

Case 8

Jessica Macnab MD, CCFP, FRCP (C)

Clinical History

This neonate presents in acute respiratory distress shortly after birth. He is cyanotic and has a scaphoid abdomen.

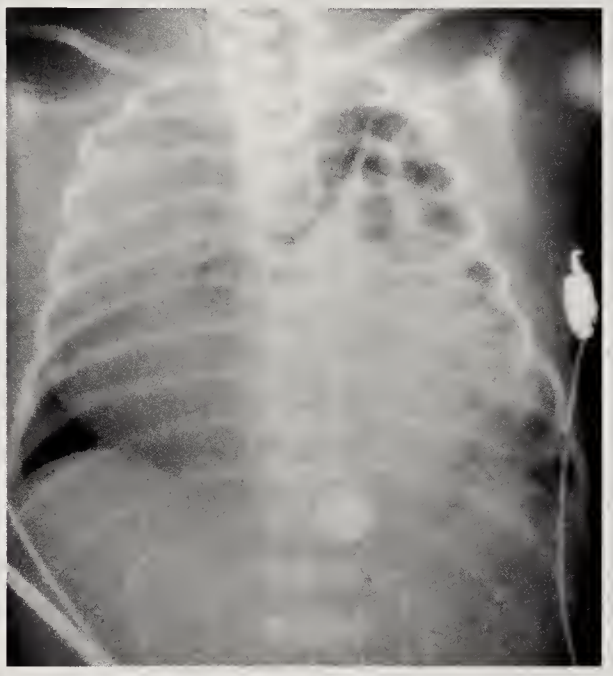


Figure 1: CXR

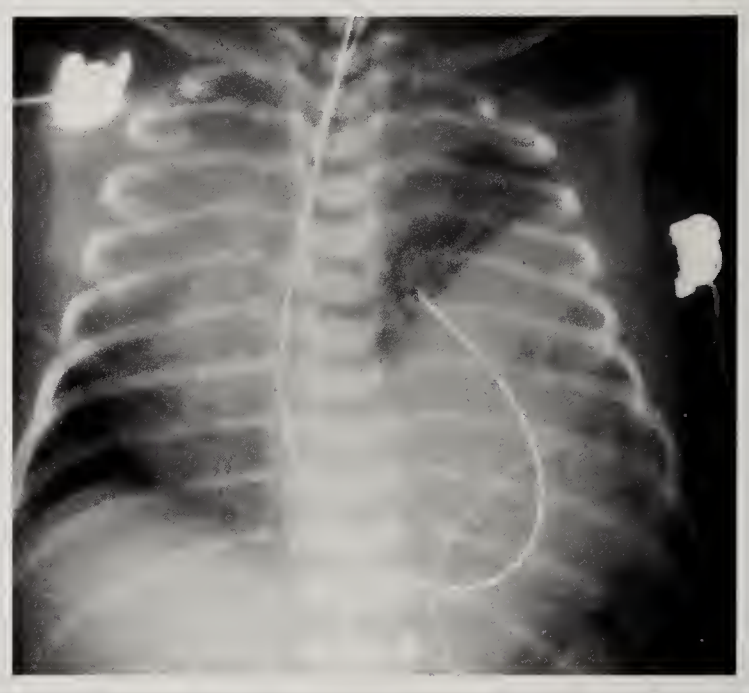


Figure 2: Plain X-ray showing NG tube.

What is his diagnosis?

Dr Macnab is a staff Emergency Physician , Sunnybrook Health Science Centre and The Toronto Hospital.

ANSWERS TO QUICK DIAGNOSIS: *(UTMJ Volume 73, Number 2, March 1996)*

Obstetrics and Gynecology Rounds

Case 1
Diagnosis: **Complete Placenta Praevia**

Case 2
Diagnosis: **Hydatidiform Mole**
Test: **Quantitative Beta HCG**
Treatment: **D & C**

Case 3
Diagnosis: **Endometriosis**

Case 4
Diagnosis: **Omphalocele**

Case 5
Investigations: **Urine C&S** **Residual Urine**
Urodynamics **Cystoscopy**
Cystourethrogram
Treatment: **Conservative**
Pessdry, Kegels
Premerin Vaginal Cream
Surgical
Vaginal: anterior/posterior repair
Abdominal/Laproscopic
Colposacropexy

Case 6
Diagnosis: **Stress Urinary Incontenence**
Treatment: **Conservative**
Kegels, Alpha Agonists
Surgical
Periurethral Fat Injections
Laproscopic Peurch

Counselling for Sexual Abuse: A therapist's guide to working with adults, children and their families

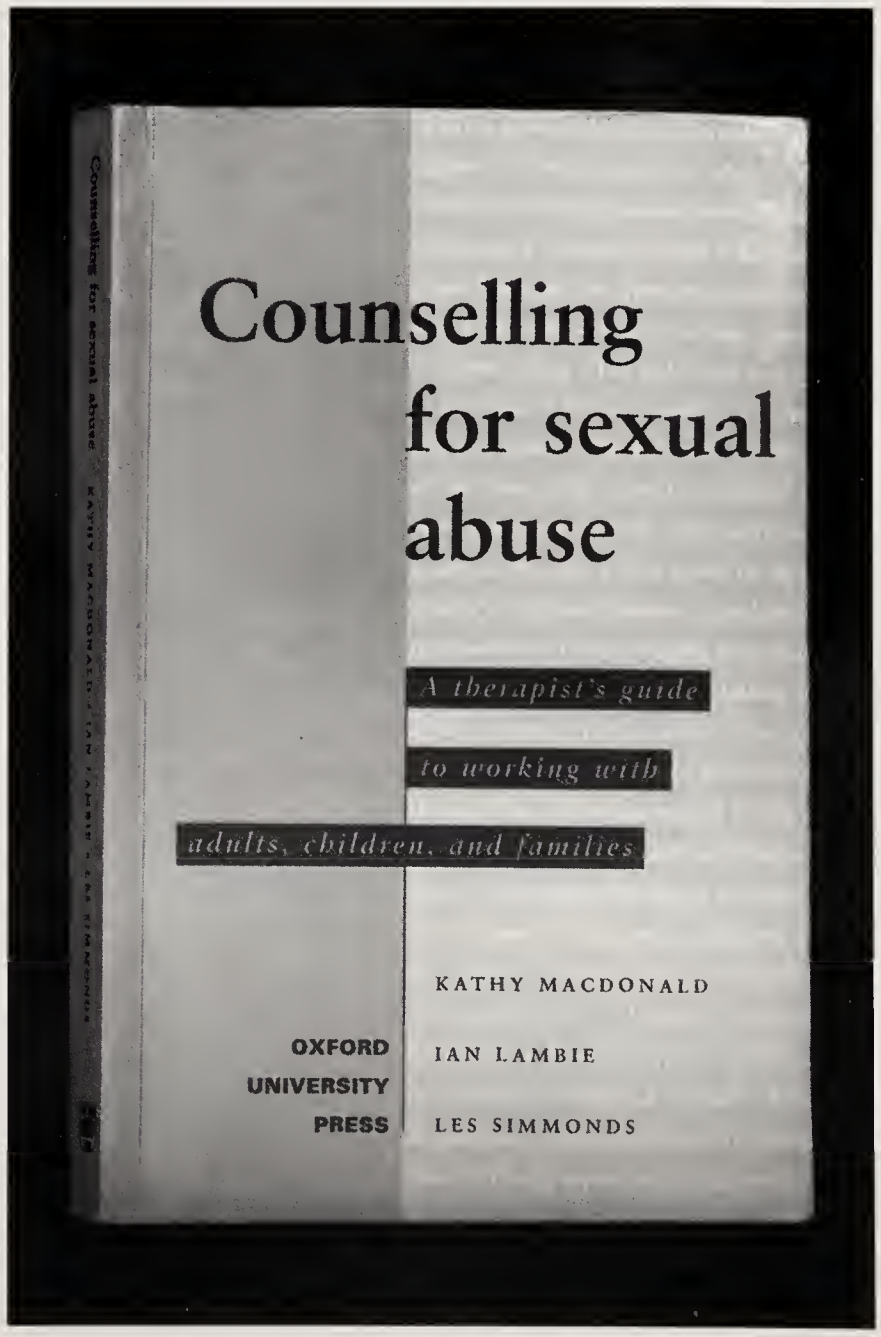
Kathy MacDonald, Ian Lambie and Les Simmonds

Oxford University Press, 1995.

The prevalence of sexual abuse in Western countries is high. Research has shown that 20 to 30% of girls and 2 to 5% of boys under the age of 16 have been the subjects of sexual abuse. Some evidence indicates that this number may underestimate male sexual abuse significantly, suggesting it approaches the levels reported in girls. Furthermore, about 25% of adult women have been sexually abused after age 16. While not all people sexually abused will suffer traumatically from the event, the majority do, either immediately after the event or events, or at some time in the future. The authors of this book, however, believe that despite these experiences, people can and do heal themselves, a process which may or may not involve therapy.

MacDonald, Lambie and Simmonds have drawn from their experience as therapistss working with adults, children and their families to produce a book which entails both a description of the effects of sexual abuse and a manual for providing therapy. While primarily directed towards people who are or will be providing therapy, the cogent and jargon-free text ensures that this book is accessible to the non-specialist. The value of this book to the majority of us who will not be counselling patients for sexual abuse lies in its ability to convince us that the trauma of sexual abuse can be successfully addressed. This book emphasizes normalcy. A significant part of therapy is convincing survivors that what happened to them is, unfortunately, normal. Their reactions are normal. And they can heal to become normal, healthy people in every way. These are important messages for health care providers too; it is important not to "pathologize" survivors of sexual abuse.

Counselling for Sexual Abuse begins by reviewing facts and fallacies about sexual abuse, and describing the basic theoretical framework in which its authors operate, drawing heavily upon family systems theory and feminism. Abuse affects the family, and the family's response in turn will have an effect on the person who was abused. Thus, counselling may involve an entire family, particularly with children. Family counselling will help the family members address their own feelings about the abuse as well as provide them with strategies for helping the abuse survivor heal. Feminist theory places sexual abuse within a societal context and encourages a moral judgment and condemnation of the abuse. Power imbalances exist along gender lines in our society and in many families; an understanding of these imbalances can help a client understand their sexual abuse in a different context, perhaps allowing them to abandon feelings of self-blame. One of the most basic tasks of the therapist is to help the child and family understand where all the blame, shame and guilt lie - with the offender. In some



situations, the child may attach blame to themselves, and parents or siblings may attach it to themselves for failing to protect the child. If the abuser is closely connected (a relative, a sibling, an uncle, etc.), some family members may be reluctant to place blame where it belongs. Other important goals of therapy are to increase the survivor's self esteem by putting him or her in touch with their strengths, dealing with negative effects of abuse, ensuring that the client has support from others, and planning for future safety.

One of the greatest strengths of Counselling for Sexual Abuse is the step-by-step guide to providing therapy for sexually abused children, adolescents, adults and their families. The tasks of therapy are clearly outlined, and many specific tools described. For example, an important task is helping the survivor talk about the abuse and express anger against the abuser. This may take different forms depending upon the age of the individual. With children, use of puppets, dolls, drawings and clay models may be appropriate tools to describe the abuse. Expressions of anger may involve cutting up , burning or throwing mud at a picture of the abuser, it may involve smashing or destroying a clay model, sticking pins in a doll representing the abuser, shouting and stomping - all physical expressions of anger which are intended to lead to a catharsis for the child. Another important task is the restoration of a sense of power to the survivor. One tool which can be used to accomplish this is a fantasy rescue scene, which provides a way in which individuals can review the abuse scene in their mind, but provide a different, happier ending. Again, different methods such as drawing, acting, writing or storytelling can be used to create the fantasy with the same empowering effect.

Finally, the authors describe another role of the therapist: advocate for social change. Through education, research, increasing awareness, government lobbying and policy changes, the authors hope that the wider society will assume responsibility for dealing with sexual abuse and the attitudes that allow it to continue. The concepts presented in this book will enable others to think and act upon this issue with knowledge and understanding.

Michèle Farrugia, M.Sc., 9T8

Cancer Biology third edition

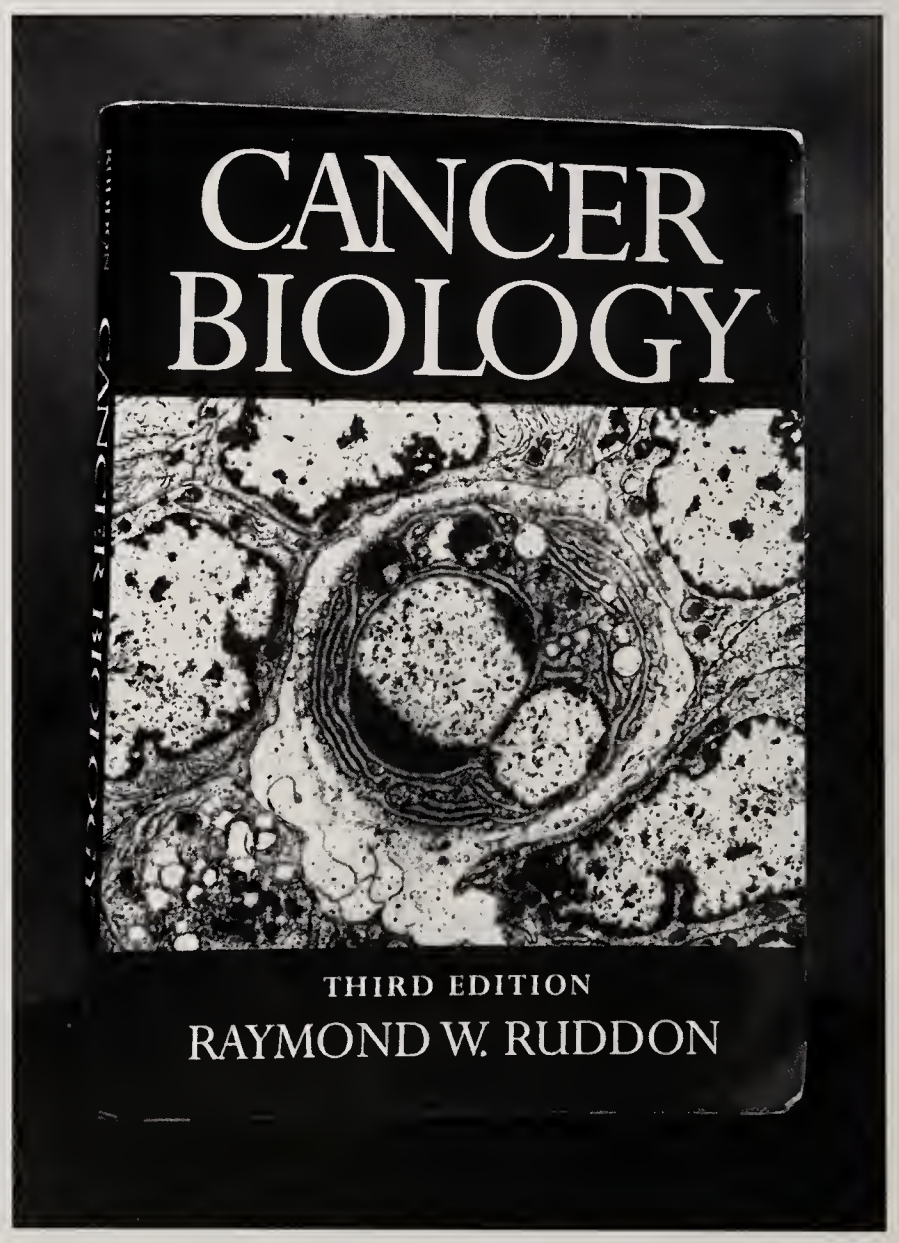
Raymond W. Ruddon

Oxford University Press, 1995

520 pp

$68.95

If you are looking for an excellent introduction to contemporary cancer research, or just wish to keep abreast of this rapidly moving field, then Cancer Biology is the book for you. This book provides an historical perspective on the major developments in cancer research and makes it possible for the reader to gain an intellectual foundation for understanding novel developments in the field. The author is able to do this by integrating knowledge from several fields of research such as epidemiology, pathology, genetics, virology, immunology, molecular biology, and cell biology, that together join to make up the fascinating field of oncology.



Cancer Biology is organized into 15 chapters beginning with characteristics of human cancer and ending with cancer prevention. The book has been thoroughly updated, extensively expanded and reorganized since the last edition. It includes new chapters on genetic alterations in cancer cells, tumor suppresser genes, transcriptional regulation, growth factors and signal transduction mechanisms, cell cycle regulation and apoptosis, tumor immunology, gene targeted therapy for cancer, and cancer prevention.

Cancer Biology is one of the few single authored text in its field. The knowledge that is presented from chapter to chapter has been well-written, well-selected, and well-integrated. A nice contrast from most cancer biology texts that are multi-authored, too expensive and too heavy to carry. I found this book to be written in such a way that students in the field can understand without necessarily having advanced expertise in a given area. The author has approached the writing of the book as if he were himself a student coming into the field.

The book is well indexed and each chapter provides an extensive bibliography (an average of 180 references) for further research. The author uses many well-illustrated diagrams and figures to complement the written text. Unfortunately, they are all black and white and since many of the figures are very intricate, the use of colour and an increase in size would have enhanced their effectiveness.

I found the first chapter of Cancer Biology to be most engaging. It provides extensive facts about cancer from micro and macroscopic features, to special diagnostic procedures and is thus a good review of the basics of cancer .

The second chapter, 'Epidemiology of human cancer", has numerous up-to-date statistics on the incidence and mortality of various cancers, their geographic distribution and the role of various factors in the development of cancer. This chapter may seem dry to all but those who are interested in the raw data. The chapters on oncogenes, growth factors and signal transduction mechanisms, cell cycle regulation and apoptosis, and tumor immunology are excellent. They provide an up to date review of some of the hottest areas in cancer research today.

As a cancer biology text, this book is clearly appropriate for graduate students and is a must for both clinicians and scientists who are actively engaged in this rapidly expanding area. The book is intended for those who wish to learn about the early discoveries that led to development of a particular field of cancer research and to know the paradigms and fundamental facts that have withstood the test of time. This book will enable the reader to become acquainted with state of the art technologies used in cancer research and to know where the field is going in the future. I would not, however, recommend this book to medical students, clerks, or other health care professionals whose sole interest is in treating or taking care of cancer patients.

Finally, as an MD/PhD student I appreciated the author's efforts to try, where possible, to show a connection between basic findings in the laboratory and clinical cancer medicine - the bench to bedside paradigm. I highly recommend this book, it is well-worth the money spent.

Ally-Khan Somani, BScH, (MD/PhD program, year 3)

Palliative Care Ethics, A Good Companion

Fiona Randall and R.S. Downie

The recognition of palliative care as a discrete branch of health care is a recent phenomenon. The original inspiration was the hospice of Medieval times, but the modern context also includes nursing homes, acute care wards and the community. As it has become clear that delivering palliative care will include more than hospice care, the expertise of people working in the field has necessarily extended into other settings. Concomitantly, there is a trend in all aspects of medical care toward increased personal responsibility with patients tending to take a more active role in their treatment decisions than they did in the past. These decisions are becoming more complex as advances in technology create new treatment modalities. This is particularly true in the field of palliative care as dying patients now have access to various controversial life-prolonging treatments. Further, these events are taking place in an atmosphere of increasing fiscal restraint. Thus, for health care workers, patients and their families, ethical issues in palliative care are becoming more complicated. Physicians will have to ensure that patients are fully informed about the myriad of options available to them, in terms of resultant quality and duration of life as well as cost. Palliative Care

Ethics, A Good Companion was written to assist in the decision-making process, and is aimed at anyone caring for someone who is terminally ill.

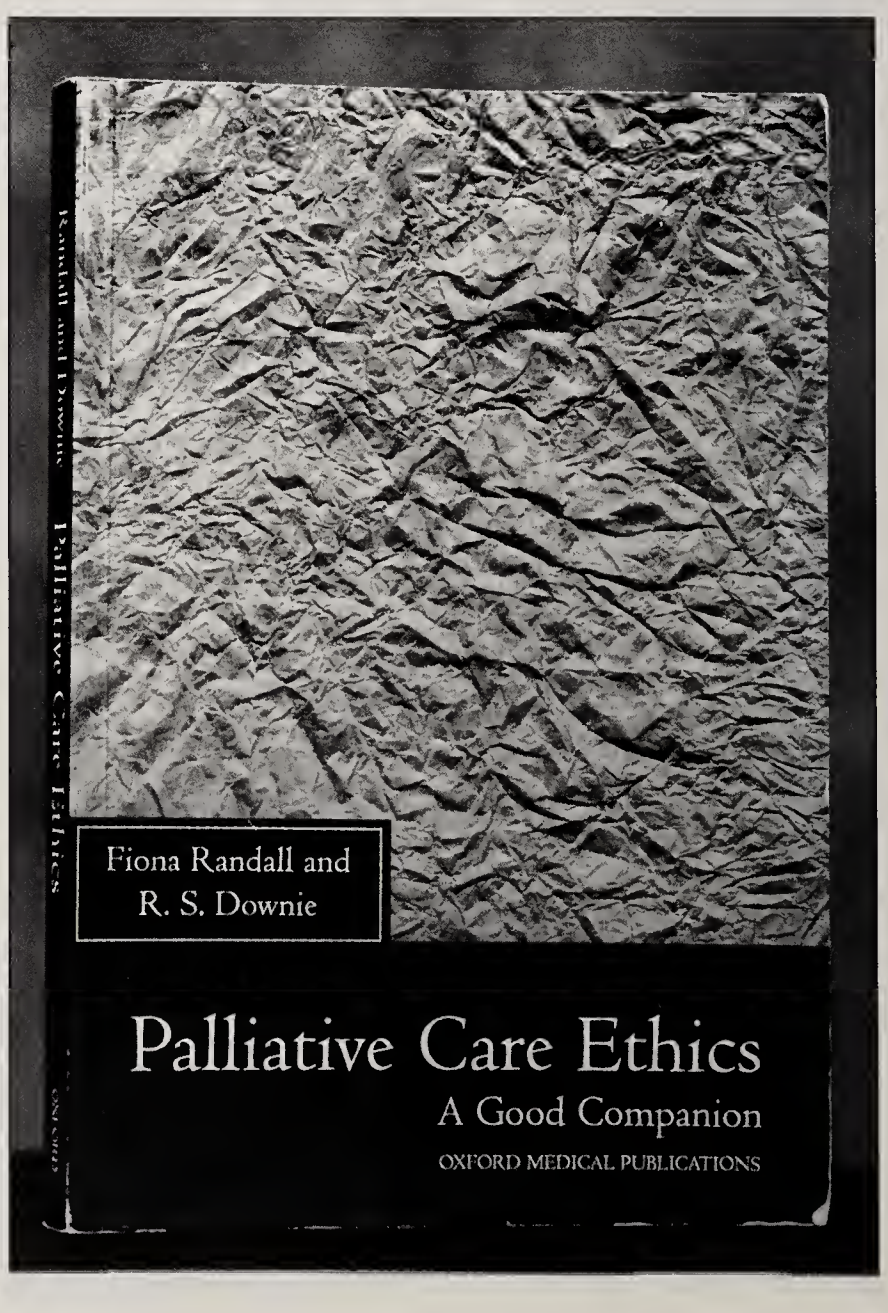
The book begins with definitions of the intrinsic and extrinsic aims of palliative care. The intrinsic aims focus on the patient's perspective of the illness, particularly with respect to suffering, while the extrinsic aims are concerned with the generation of an algorithm in which caregivers interact with the patient. These two aims should fuse to engender care that is holistic in nature. The importance of adhering to this concept is re-iterated repeatedly throughout the book, however, the way in which it was initially introduced was not terribly effective. Rather than exploring these aims from the perspective of professionals in the field, patients or family members of patients, the discussion was from a philosophical and historical viewpoint, which served to complicate the information. In the present climate, with so much discussion in the popular press, viewing palliation from a purely theoretical perspective can only alienate health professionals from their patients.

This complexity of language and the fact that the authors' perspective was removed and theoretical, was evident throughout the book. It was particularly apparent in the chapter in which the patient-care-giver relationship was examined using various models. In the current North American climate of patient autonomy, care decisions are made jointly by patients and care givers and the traditional model of benevolent paternalism has fallen from favour. The conclusion of the discussion in the book is that neither approach is satisfactory, because while the historical method of "doctor knows best" is clearly unacceptable today, the new models of autonomy are also inappropriate due to the knowledge gap that exists between patients and physicians. This does not seem to be in keeping with the current philosophy in this country, in which caregivers are required to give patients and their families all the information and assistance they need to make well-informed decisions themselves. The authors alluded to this perceived power differential between physicians and patients throughout the book.

Palliative Care Ethics, A Good Companion provides a thorough summary of the issues facing practitioners of palliative care. The value of the team approach was discussed at length, although it may have contained excessive rationalization of a conceptwhich already exists in our hospitals and is currently employed by health care workers. The discussion of conflicts and resolution, collective decision making /responsibility and emphasis of the team as a patient-centred entity were effectively addressed. This is particularly important in palliative care where emotions run high and strong personal biases often exist. Equally helpful was the discussion of the clinical decision-making process, in which the unique aspects of palliative care decision-making were emphasized. These include the unpredictable outcomes of palliation, the paramount importance of the patient's wishes, the competence of the patient to make decisions and a discussion of the distinction between killing and letting die. Confidentiality, medical treatment versus medical care, life-prolonging treatments, the role of the family and emotional aspects of palliative care were also examined at length in an interesting and effective manner. The last chapter, dealing with resource allocation, has particular resonance in these times of fiscal restraint and cost cuts in the health care system.

While this book would serve as a thorough reference for practitioners of palliative care, unfortunately, the verbose and rather dry manner in which the information is presented makes it somewhat difficult to read. Consequently, it will probably be reserved for those with a more theoretical interest in the subject, such as medical ethicists, rather than for the health care practitioner.

Karen Gronau, MSc, 9T8



Infection and Immunity

John Playfair

Oxford University Press, New York, 1995

154 pp

$25.95

Infection and Immunity describes the human immune system and how it works to combat infectious agents. The topic of human infections is multi-disciplinary and this book attempts to bridge these areas which include microbiology, immunology, pathology, pharmacology, epidemiology and medicine. Because of the overall set-up of the book, it is certainly not exhaustive in terms of the number of topics and the depth of coverage. The book has 20 chapters, which average 4-5 pages in length. While each chapter consists of only a few pages, the author has done a good job of providing a very brief and simple, though superficial, 'bird's-eye view' of the subject.

The format of the book follows that of actual lectures and tutorials given at University College, London. The chapters are easy to read and are written in everyday language with scientific terminology clearly explained. The various topics like natural immunity, antibody responses, cell-mediated responses, autoimmunity, and immunodeficiency are introduced and developed in a story-like fashion that is occasionally overly simplistic. In fact, the book is written in such easy-to-understand format that even those with no background in the sciences can follow and comprehend. This is consistent with the author's intention which was to summarize the essentials of infectious diseases in a way that can be understood by "any student or potential student of science or medicine, including . . . the interested lay[person]". This book is perfect for those with no knowledge of immunology and infectious diseases. For those with some background in these areas, however, this book is not quite comprehensive enough and would be uninformative, especially with respect to dealing with immunological mechanisms, theoretical explanations, practical and clinical applications, and recent advances.

Infection and Immunity has four self-testing tutorials which help the reader to assimilate the information by answering thought-provoking essay questions. Examples of the essay questions are: "Recognition of foreignness; the more specific the better. Discuss."; "Most autoimmunity is due to infection. Discuss."; and "What is 'natural' about natural killer cells?" Helpful sample answers to the questions are also provided. The author acknowledges that his book provides a superficial overview of the material and he provides a list of other books which would be useful should the reader wish to delve deeper into the subject matter.

With an index that is easy to use, Infection and Immunity is very user friendly - especially for readers new to the topic of infectious diseases and immunology. There are numerous tables and schematic diagrams used to illustrate key concepts in each chapter. These would make for excellent summary guides or study aids. Unfortunately, the book does not have any colourful illustrations of what the infectious agents and the diseases that they cause look like. The appendix includes 10 of the more well-known infectious diseases, such as influenza and schistosomiasis, each with a paragraph describing the related immunological features.

At Cdn. $25.95, Infection and Immunity is quite expensive for a short, soft-covered book. For a few dollars more, one could invest in a more comprehensive immunology textbook that provides more depth and coverage of topics. For the medical student not wishing to spend time using dense and detailed textbooks however, a book like Infection and Immunity just might do the trick.

Charles Dela Cruz, BScH (MD/PhD program, year 2)

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